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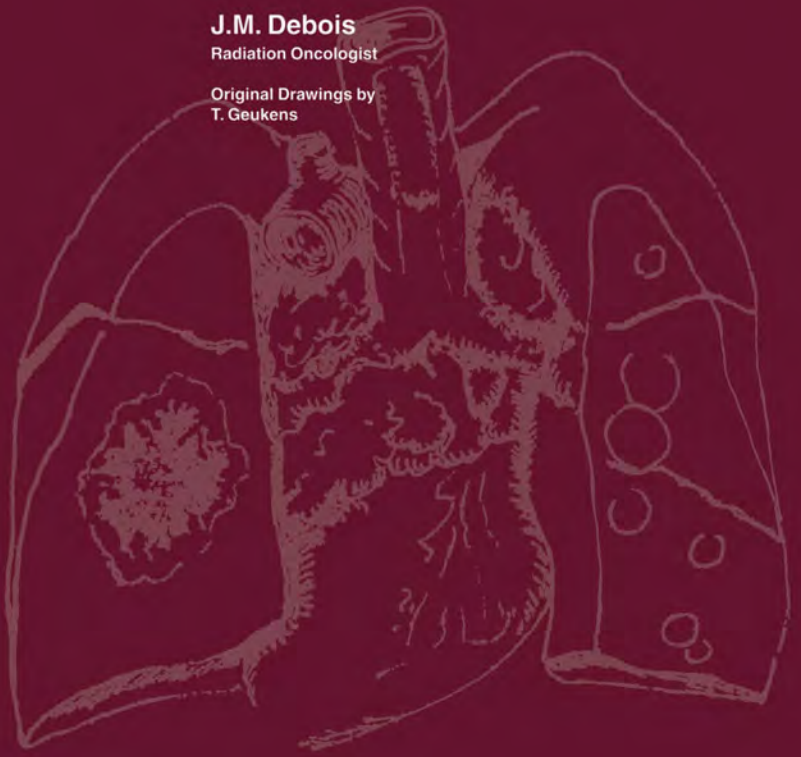
The Anatomy and Clinics of Metastatic Cancer

J.M. Debois
Radiation Oncologist

Original Drawings by
T. Geukens



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The Anatomy and Clinics of Metastatic Cancer

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Dr. J.M. Debois

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I dedicate this book to
Doctor James Paget (1814-1899)
He was the first to observe the
non-random nature of the metastatic process
Reproduced by kind permission of
the President and Council of the Royal College of Surgeons of England

I must acknowledge

- the continuous support of my wife Kristin,

- the encouragement of Prof.Marc M.Mareel, M.D.

- the artistic devotion of colleague Tony Geukens, MD.

- the endeavour of the Editorial Staff of Kluwer Academic Publishers

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FOREWORD

by Prof.Dr.M.M.Mareel
Head of the Department of Radiotherapy and Oncology
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Invasion into neighbouring tissues and metastasis to locoregional lymph nodes or to distant organs are responsible for most of cancer deaths. This well-established clinical fact has stimulated fundamental research about the mechanisms of cancer invasion and metastasis. One of the goals of this effort was the elaboration of new rationales for the treatment of cancer patients. Since the fifties, there has been a growing interest in metastasis research and the advent of the more recent biotechnology has added molecular dimensions to this research. Numerous papers have appeared describing the results of experimental work, comprehensive reviews can be found in high-ranking journals and several monographs have been written by pioneers in the field.

What is however hard to find is an extended account on the clinical aspects of metastasis. This gap is filled by the present book, written by an experienced radiotherapeutic oncologist who has been facing the clinical problems of metastasis almost daily for several decades. Part 1 of account categorizes metastases by their site of clinical appearance and asks the question where they originate from. Part 2 categorizes primary tumors by their organ of origin and asks the question where they metastasize. The book is a rich source of more than 12.000 references of case reports, regular papers and reviews from cancer and non-cancer journals that are on the citation lists or not and many of which escape from our current methods of literature search. The present encyclopedic work contains a wealth of useful tables and schematics. The approach is merely clinical with emphasis on diagnosis. It is, nevertheless, our opinion that the present book is of interest to both clinical oncologists and cancer researchers. The former will be assisted in the diagnostic work up of their cancer patients and data on the probability and multiplicity of metastases will provide them with better rationales for treatment. The latter are offered an exquisite document to test the relevance of their experimental data for human cancer.

Gent, October 24, 2000

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THE ANATOMY and CLINICS of METASTATIC CANCER

PART I - THE METASTASIS AND ITS PRIMARY

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TxNxM1
The Anatomy and Clinics of Metastatic Cancer

INTRODUCTION

In the great majoprity of cases, the metastases causes the patient's death. Currently, every effort is being made to detect the tumor before metastases should be settled, as cure is obtained more frequently at that stage. Early diagnosis is a first step towards definite cure.
TxNxM1 is the clinical code stating that metastases are present. The presence of metastases however is characterized by an enormous number of different situations, not to be recognized by the only setting of M1.
The daily practice of oncology is concerned with the detection of any metastasis, the establishment of a certain patttern for each primary and what the clinical symptomatology of each site is. It is very strange that almost no single book is dedicated to the clinical evaluation of metastatic disease, in view of its almost unlimited clinical presentation.

I developed an interest interest in the clinics of metastases several years ago. During my radiotherapy-oncology career, I was confronted many times with 'unexpected' metastatic locations and manifestations. This sharpened my attention and particular interest for the literature reports on the subject.
The spread of the reports in journals of almost all particular disciplines, from dermatology to ophthalmology, from orthopedics to neurology and others, even forensic medicine, aside the specific oncology, has resulted in the fact that many case reports or even reviews on any location are hardly within reach of the practicing oncologist, in spite of available online databases. The knowledge on metastatic diversity is indeed spread over medical journals of almost all disciplines.
We have tried to bring together the relevant information concerning incidence, symptomatology, pathology, diagnosis and imaging. Treatment problems are not discussed, in view of the fast evolution of treatment methods applied for the several clinical situations. The work focuses on diagnosis and its various sections try to reinforce the message that the clinician, and the oncologist in particular, must remain aware that the many situations and problems encountered in the referred patients could well involve a metastatic process.

In the last decades, aggressive treatments have been developed for solitary metastases. It is therefore important for the oncologist to know how the patient should be evaluated futher. So Ml is more than just a definition on the presence of any distant metastasis.

The work is divided into two parts. The first concerns the organs and sites where the metastatic cells settle. When a metastasis is encountered anywhere in a 'receptor' organ, which could be the primary ?
In the second part, we discuss the pattern of the metastases from the different primaries. Where can a metastasis be expected from the 'emitting' organ ?
Nevertheless, during the follow-up and/or further evolution of the neoplastic process, unexpected locations of metastases can cast difficulties in the judgement of the clinical situation and further diagnosis. The differential diagnosis with a second primary is then necessary.

CLINICAL TIME SEQUENCE

As every clinician knows, metastases can appear at several phases of the evolution-history of the tumoral process. While many reports clearly relate the appearance of the metastases with the life-time of the tumor, no single author has considered the possible difference in characteristics of the metastases in these different phases on the incidence, nor has classified them.

On the basis of the time sequence related to the evolution of the primary, metastases can be divided in a number of time-groups (table 1). There are inherent problems in the detection of the different types and each is significant in a different way.

Table 1 - Type of Metastases timely vs Primary Tumor

Type 1 :	Metastases as first presentation
Type 2 :	A. clinically present at diagnosis of primary
	B. found during any staging procedure
Type 3:	Metastases during follow-up
Type 4:	Metastases detected only at autopsy

The first and least frequent type concerns metastases presenting before the primary is known. They can be considered as 'alarming' or revealing metastases. This is a most challenging situation for the clinician, who should not miss this difficult diagnosis, as nature can be very misleading.
The second type or type 2 consists of metastases found simultaneously at presentation and at diagnosis of the primary. They are either clinically detectable, confirmed with staging (imaging, fine needle cytology or biopsy or surgical) or detected with staging procedures. They dictate the kind of treatment and the prognosis and have another significance than type 3-metastases, which become manifest later during follow-up either clinically or by sequential staging procedures. They can occur early or late after the treatment of the primary and must be distinguished from a

new primary. Finally, one can find other metastases, unknown or silent during life, at autopsy. We call them Type 4 metastases. These metastases can infer statistically on the rules of staging procedure, but have no further clinical implications.
Metastastases in any organ will develop depending on the vascular anatomy, the bloodflow, the 'seed and soil' parameters and eventually specific receptors. The book will discuss only the anatomy and clinics, without the latter parameters.

The 'correct' meaning of metastasis is a distant and anatomically independent seeding from a primary tumor (μετα-ιστημι : meta-isthemi, I send away). This means that cells are sent 'far' away from the primary and will eventually lodge and grow somewhere else, brought there across the vascular, arterial, venous system and the lymphatics.
While the soil aspect has been much discussed, it is nevertheless necessary that there be mechanical spread of the metastatic cells for them to reach the different sites. The two theories on metastatic spread cannot be separated for the process and are in fact two aspects of the whole.

Reviewing the literature reports on metastatic situations, one can remark that different situations are in fact mixed together, although the distinction is made in a number of reports.

Another situation also described as a metastasis is the ingrowth of an organ by neighbouring metastatic lymph nodes.
Finally an organ can be invaded by a tumor originating in a neighbouring organ (table 2).

Table 2
Different Clinical Situations described as Metastasis

H or hematogenous spreading
L or invasion by metastatic lymph nodes
C or contiguous invasion from a neighbouring organ

The Metastatic Circle

We will take for granted that the reader is familiar with the usual routes followed by the metastatic cells spread throughout the body. A summarizing diagram according to the principles set by Gilbert (Fig.l), shows the most common relationship between a tumor in a certain organ and the metastatic sites. We will not discuss the mechanisms of metastases either.

Literature

The literature references were collected since many years from Current Contents, Philadelphia, or recently via PubMed, the database of the National Libray of Medicine in Washington, D.C., USA. Many authors provided us with reprints. The literature references in these articles were carefully checked and added to our data base, now containing about 12000 references concerning metastases (Pearl growing method).

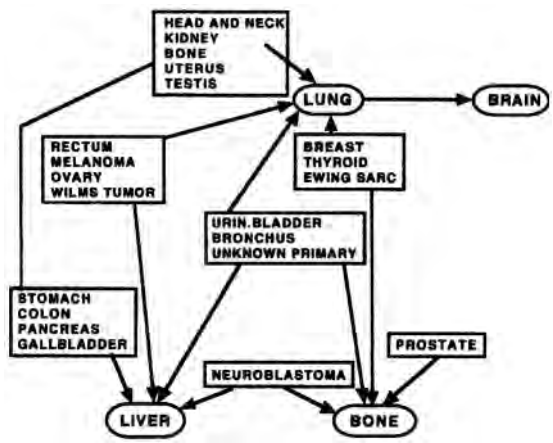

Fig.1 -The Metastatic Circle according to Gilbert

The original articles were not all found, as many are rather old and the concerning journals not available in the consulted libraries or unreadible as written in Japanese and other non-western languages. Other journals were not available in the several libraries we consulted.
We looked for the number of reports of each heading, reflecting in a way the incidence of different sources and sites of metastases. It should be reminded however that unusual or rare cases are more prone to be reported than 'common' cases.
Reference to textbooks, unless classical, to congress and other 'intermittent' publications, who are difficult to reach, were omitted.
We closed the database of the journals at Feb.2001. In the reference lists included, we enclose mainly those after 1974.

Dr.J.M.Debois
Radiotherapist Oncologist (retired)

LIST of ABBREVIATIONS

CNS	Central Nervous System	FNAB	Fine needle aspiration biopsy	PET	Positron Emission Tomography
CPA	Cerebello-Pontine angle	FNAC	Fine needle aspiration cytology	TNM	Tumor-Node-Metastases-classification/staging
CT	Computer Tomography	M50	Man aged 50 years	UICC	Unio Internationalis contra Cancrum-Classification
F50	Woman aged 50 years	MRI	Magnetic Resonance Imaging		
FDG	Fluoro-deoxy Glucose	NOS	Not otherwise specified		
FIGO	Federation Internationale de Gynécologie et Obstétrique				

1
METASTASES to the THORAX

This chapter covers the metastases to the lungs, the bronchi (called endobronchial metastases), the pleura, the heart and pericard, the thymus, the diaphragm, and the mediastinal nodes and the breast.
Metastases in the esophagus are described in the chapter on the gastrointestinal tract.

METASTASES to the LUNG

What is commonly described as metastases in the lung can be divided into four clinical situations.
First, the classical parenchymal lung metastases is the most frequently occurring situation. Two variants of it are the lymphangitis carcinomatosa and the acute or sub-acute multiple tumor embolic situation.
Secondly, there are the tracheo- (endo)-bronchial metastases, a rare but probably under-reported situation.

Metastatic cells can reach the lungs by five routes:
- hematogenically through the arteria pulmonalis;
- lymphangitic spread, probably from the mediastinal nodes;
- tumor embolization through the arteria pulmonalis;
- direct extension from the tumor, for example, from the chest wall and breast;
- embolism of mucin.

PARENCHYMAL LUNG METASTASES

Incidence

The lungs are the commonest site of metastases for many primary tumors. There is, however, a large difference in propensity between the various tumors. It is just as high at autopsy with more than 90% in melanomas.

The lungs serve as first filter for tumor emboli in malignancies whose venous drainage flows directly into the lungs without first passing another filtering organ. The tumors of testis, melanoma, osteosarcoma, and head and neck tumors have the highest incidence of pulmonary metastases in the absence of other distant metastases. Its incidence is lower for the other primaries (table 1.1). Due to the relative low proportion of the former malignancies, the overall incidence at autopsy oscillates around 30%.
It is obvious that these data are only indicative, because, first, stage at diagnosis is an important factor. Nevertheless, they give a good impression of the wide range. There are further differences depending on histology type.

Table 1.1 - Metastases to the Lung
Frequency for different tumors at diagnosis and at autopsy (From Whitesell et al.)

	At diagnosis	At autopsy
Choriocarcinoma(*)	No data	70-100%
Testis	2-12%	70-80
Osteogen.Sarcoma	15	75-95
Melanoma	5	66-80
Thyroid	4-10	65
Breast	4	60
Kidney	5-30	50-75
Colon-Rectum	<5	25-40
Bladder	5-10	25-30
Stomach	No data	30
Head-Neck	2-5	13-23
Cervix uteri	<5	20-30
Liver	No data	20
Prostate	5	13-53
Ovaries	<5	10

(*) since these data were reported, CC is now being cured in more than 90% of the cases

The extrathoracic tumors metastasizing to the lungs can be divided into three groups (Coppage et al.).
1. Tumors with a venous flow direct to the lung: melanoma, sarcomas, thyroid, kidney, testis, adrenal and head and neck;
2. Tumors seeding first other organs, either the portal system or the venous para- and intravertebral plexus of Batson, the abdomino-pelvic tumors;
3. Tumors that seed the lungs and other organs independently, such as the kidney, the breast, rectum, bladder and uterine cancers.

Pathways

Parenchymal lung metastases invariably arise from tumor emboli arrested in the small pulmonary arteries. The tumor cells are arrested in the pulmonary arteries sized between 400 and 800 μm in diameter. Occa-

sionally widespread occlusion happens in medium sized arteries, tumor-associated thrombi or intimal hyperplasia provoked by the tumor. The vascular occlusion can be so extensive as to cause pulmonary hypertension with right-sided heart failure. In acute circum-stances massive tumor embolism may be fatal (see further).
Bronchial arterial dissemination is far less common but could account for bronchial metastases.

The lungs receive arterial blood at a rate 16 times higher than the liver per gram of tissue, but there is no correlation to this in the number of metastases (Salsali et al.).

Site

In spite of the great number of reports on surgical resection of parenchymal metastases, virtually no data have been reported on the site distribution of metastases within the lungs. While these series are moreover skewed towards low numbers of metastases, even then no anatomical distribution has been reported.
Some authors state that the metastases affect more the lower lobes, but this is not quoted by most authors.
According to Willis, earliest distribution is frequently peripherical or subpleural. He found more solitary metastases in the basal regions than in the apical. Confir-matory data are however lacking.

In an autopsy study of 56 unselected oncology-patients, Crow et al. found metastases in 30 patients, or 54%. In 9 patients, the metastases were detected only by histology. They report 317 radiologically visible metastases in 21 patients or about 15 per patient. About two-thirds (60%) of the metastases were pleural or subpleural and a further 22% in the outer third of the radiographic lung field. This corresponds with the fact that most metastases are located in the periphery, at the end of the pulmonary arterial system.
From an autopsy study on 24 patients, Scholten et al. showed that more than 90% of the parenchymal metastases were located within the outer third of the lungs (table 1.2).

Table 1.2 - Parenchymal Lung Metastases
Autopsy data (N=24) Scholten et al. 1977

Subpleural	67%
Outer third	25%, together 92%
Middle third	4%
Hilar	3%

On the other hand, Salsali et al. found that for peripheral sarcoma metastatic to the lung, over 80% of the metastases were within the upper zones of the lung. The explanation is probably that the upper lobes do not expand very fully in normal setting, so that the ventilation and perfusion are not as efficient. Particles within the lung alveoli and in the blood circulation are not eliminated rapidly enough. It should be remembered that tuberculous lesions and even lung carcinoma are more frequent in the upper zones.
A predilection for a more basilar distribution is consistent with the increased blood flow in that region in the upright position (Greelich et al.). How far gravity has an influence is unknown. A peculiarity is the predilection of choriocarcinoma to metastasize more in the posterior portion of the upper lobes. This has been ascribed to the long supine position during parturition and eventually resection surgery (Hensin).

Pathology

Metastases in the lung presenting as discrete nodules may be solitary or multiple and bilateral. Both lungs appear to be equally affected, although data are in fact absent in the literature reports. Minor states that in his series of nearly 200 patients, there were more metastases in the right lung. This was found for almost all primaries. Similar pertinent data were not found. Some comparative patterns between a number of primaries are outlined on table 1.5.
Contrasting with primary bronchial tumors, metastatic nodules have well-circumscribed margins. Their shape is mostly spherical except when subpleural. They are then stellate in shape or plaque-like (Willis). On a cut surface they are generally white and opaque, and can show necrosis and/or hemorrhage. The ensuing cavitation is however not present in all tumors.
Size ranges from a few millimeters to several centimeters. The largest are seen in sarcomas.
In an evaluation of a large series, Gross et al. found that 87% of the lesions of more than 2.5cm in diameter were metastatic. Approximately 75% of the secondary malignancies in the lung present with multiple lesions. The consequence is that multiple lesions are metastatic in 73% of the cases. They point out that neoplasms of the alimentary tract were the most common primary, but data were not given.

A special form is miliary carcinomatosis, which consists of myriads of small nodules. This must result from a neoplastic invasion of a systemic vein, even of the thoracic duct, from where a shower of tumor emboli is discharged to the lung. Making a distinction with lymphangitic carcinomatosis can be difficult.

Most metastases of carcinoma or sarcomas are white in colour and firm and uniform in texture. The appearance rarely permits identification of a specific nature (Willis). The mucoid adenocarcinoma can contain gelatinous deposits, the melanoma metastases can present with grey or black color. Choriocarcinomas are typically multicolored mottled white, yellow, brown, red or grossly hemorrhagic.
Ossifying metastases are described in osteosarcomas and others (table) with areas of dense osteoid tissue or even fully formed bone (Willis).
At microscopic examination, the growing edge will

show the type of spreading of the tumor.
Three patterns have been described for the intra-pulmonary dissemination. The pattern governs the radiologic appearance.

1. The tumor grows into the lumen of the neighbouring alveoli and extends into the next air space;
2. The tumor grows within the interstitium of the alveolar septa which become thickened. Air spaces can be obliterated resulting in destruction of its architecture with intra-alveolar growth;
3. The tumor spreads along the surface of the alveolar septa, replacing the epithelium. The lining is seldom more than one cell thick. The alveolar space or the air space are not obliterated. This pattern is common for the bronchiolo-alveolar carcinoma, but occurs also in some adenocarcinomas of the pancreas, the stomach and rectocolon.

Vascularisation

The vascularisation of the pulmonary metastases has been studied by a number of authors. By making comparisons of post-mortem angiography and histologic investigations, Reitemeyer et al. found that the favoured point of metastatic growth were the peripheral parts of the pulmonary system, especially the terminal arteries and praecapillary arterioles. Newly formed irregular vessels were observed within the metastatic growth. Angiography shows connections between these vessels and the pulmonary artery system. Overall, the pulmonary artery is the main blood supplier of the metastases. Other authors have shown connection with the bronchial vascular system in vivo. Milne thus states that pulmonary metastases in the perihilar areas may be supplied by bronchial arteries. If at arteriography a lesion has pulmonary arterialisation, it is very likely to be metastatic. Primary bronchial carcinoma have usually a bronchial and pulmonary artery supply.

Table 1.3 - Pulmonary metastases
Tumor types possibly presenting with calcification

Primary calcifications	Secondary calcification
Osteosarcoma	after hemorrhage
Chondrosarcoma	after necrosis
Synovial sarcoma	due to treatment (RT-chemo)
Fibrosarcoma	Choriocarcinoma
Mal.Mesenchymoma	Hodgkin's disease
Thyroid cancer (pap.-foll.)	Teratoma testis
Ovarian cystadenocarcin.	Prostate cancer
GIT mucoid adenocarcinoma	
Breast mucinous adenocarcinoma	
Pulmonary carcinoids (peripheral)	

Particular Morphology

Calcification of pulmonary metastases has been described in several situations and is observed at CT in about 7% of bronchial cancers (Khan et al.). It can be inherent to the histology type of the tumor, but can also be secondary possibly after an hemorrhage, or necrosis either spontaneously or following treatment (table 1.3). Calcium can also be deposited in mucinous secretions of adenocarcinoma (Khan et al.).

Spontaneous cavernous formation of the metastases is rare: about 4% according to Dinkel et al. This is caused by central necrosis in fast-growing tumors or presently more frequent due to the different treatments. The formation of cavernous cavities at the subpleural site can lead to spontaneous pneumothorax. The size of the cavernes ranges from 0.5 to several centimeters. Spontaneous pneumothorax is rarely reported. In 1976, Wright found 54 cases in the literature. It is remarkable that 41 of them concerned sarcoma-metastases of all types. Reporting on spontaneous pneumothorax occurring during chemotherapy, Stein et al. found 22 cases, of whom only 6 were sarcoma, but the other tumors were mainly Wilms' and testicular tumors, but also bronchial and other rare tumors such as ovarian granulosa, thymoma and others.

Of 1100 cases of spontaneous pneumothorax, only 10 were due to a malignancy either primary or secundary. Half of them were sarcomatous metastases and 8 of the 10 patients were men (Dines et al.). Cases have been reported where the pneumothorax was the first symptom as in a choriocarcinoma presenting 5 years after an aborted pregnancy (Ouelette et al.).
Reporting on one case in a seminoma-patient, Srinivas et al. reviewed the literature and could list the various causes of pneumothorax in malignancy (table 1.4).

Table 1.4 - Spontaneous Pneumothorax in Malignancy
Modified from Srivinas et al.

Causes	Possible Mechanism
Tumor invasion	Broncho-pleural fistula
Invasion of pleura	
Vascular invasion	
Tumor shrinkage	Shrinkage of subpleural
Chemotherapy-related	tumor
Radiation	
Spontaneous necrosis	
Mechanical effects	Check valve mechanism
Bronchial obstruction	Rupture of subpleural bleb
Tumor embolus	
Contributing factors	
Defective repair mechanism	
Severe emesis	
Secondary infection	
Instrumentation	

The phenomenon of cavitation has received much attention in earlier literature. Reviewing the literature up to 1961, Dodd et al. found 43 cases reported, originating from different primaries, without any specific preference. They added 14 cases, found from 121 cases with pulmonary metastases or 11.5%. They are single or multiple. They found that the cavity walls were composed by a mixture of fibrous tissue with well-differentiated squamous carcinoma cells. This is in contradiction with the necrosis hypothesis.

Table 1.5 - Comparative features of Pulmonary Metastases according to the type of primary tumor
Modified from Filderman et al.

	Incidence-Type	Pattern of spread	Radiographic pattern
Melanoma	60-70% pulmonary 28% pulm. and pleura <2% solitary 7% lung only	Mostly detected 4-6 mo after diagnosis of primary	Multiple 40% Solitary 20% Miliary 1.5% Diffuse: unusual
GermCell tumor	Testis: frequent, more in seminoma ChorioCarc: frequent	Seminoma: lymphatic ChorioC : hematogenous in late stages	Testis:single or multiple some endobronchial 'cannon balls' ChorioC: hemorrhagic
Prostate	at autopsy: 20-25% clinically : 5-10%	Unusual without bone Both hematogen-lymphang.	Solitary, evolves to multiple or lymphangitic
Kidney	at autopsy 55-75% in 30-45% no renal symptoms	Hematogenous Lymphangitic towards mediast. and also hilar lymh nodes	Endobronchial Nodular Lymphangitic Large vessel thrombi
Rectum-Colon	at autopsy 14% more from rectum>colon more from right>left colon	Some with mediastinal and/ Hilar nodes Hematogenous Colon: solitary rare with liver	Single or multiple nodules Endobronchial - tracheal
Thyroid	depends on histology most anaplastic and early papillary first cervic.nodes follicular bypass node to lung Overall 10-25%	Hematogenous	Single or multiple nodules macro- or micronodular
Pancreas	at autopsy 'after liver' Tail >> body or head more in undiff.type	40-62% pleural lymphatics Retrograde lymph.invasion	Solitary Bilateral multiple w.pleura Cavitating type
Liver HCC	at autopsy 37-70% silent in 50%	Hematogenous Lymphatic spread venous thrombosis- heart	Scattered nodules Pleural effusion Many in right lower lobe
Ovaries	+ pleura >50% depends on site, histology and stage	Intrathoracic nodes +pleura in >40% Hematogen and lymphangit after peritoneal spread	Parenchymal 28% Intrathor.LyNo 11% Pleural metast 7.5% Lymphangitic 6% Endobronchial rare Lung only very rare
Cervix- Endometrium	at autopsy <50% Cervix> endometrium most in advanced disease adeno cervix>epidermoid	Orderly lymph..hematogen.	Multiple Solitary 30% Cannon-ball-Cavitation poss. Endobronch.reported
Breast	(direct invasion) lung solely 15%, pleura 10% with bone 56%	direct invasion lymphangitic hematogenous	Parenchymal nodule Lymphangitic spread pleural effusion endobronchial
Head-Neck	autopsy: 24% lymphangit autopsy: 5-30%, depends on site of primary DD. second primary frequent	Rare without cervical nodes	single or multiple nodule may cavitate
Sarcoma	at autopsy >90% depends on hist.subtype within 2 yrs of diagnosis	Hematogenous	Solitary rare usually multiple and large can cavitate, usually more than visible on RX

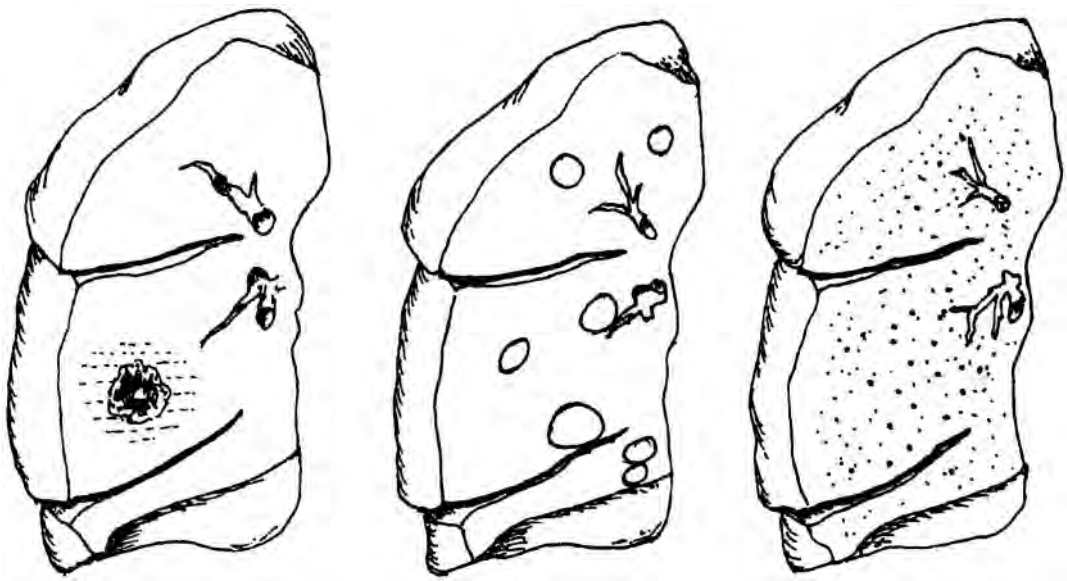

Fig.1.1 - Schematic examples of different pulmonary mestastases. at the left: middle lobe metastases with pulmonic condensation and central cavitation; in the middle: typical image of 'cannon-balls'; at the right, image of miliary metastases 'snow storm'.

In a fresh look at the problem, Chaudhuri et al. found 25 cases in their files, of whom only 8 were single. The majority of the primaries were colonic (8) and bronchial cancers (4). A literature review in 1970-75 disclosed other cases (table 1.6).
In the meantime cases of pancreatic and urinary bladder carcinoma have received some attention.

Table 1.6 - Pulmonary Cavitating Metastases
Primary Tumor involved - Literature Review
(Chaudhuri et al. N=75 and other recent cases)

Head and Neck	10	Skin	1
Breast cancer	10	Urinary bladder	4
Thyroid	2	Testis	1
Bronchial	9	Cervix uteri	5
Mediastinal	1	Female genitalia	5
Pancreas	2	Penis	1
Recto Colon	20	Kidney	2
Esophagus	1	Anus	1
Stomach	2	Not stated	19

Cavitating pulmonary metastases are particularly common in mucus-secreting adenocarcinomas, presumably due to the continuation of mucus secretion. Furthermore, the authors noticed that the metastases from head and neck tumors showed earlier and more extensive excavation than those of genitourinary tumors. Reporting on 9 cases with spontaneous pneumothorax, Wright mentioned a relationship between cavitating metastases and spontaneous pneumothorax. Reviewing the literature, they retrieved 89 reported cases of cavitating metastases (1976). They found more tumors of the uterine cervix, rectocolon and various sarcomas and indeed, also a high number of H&N tumors.

A mechanism for the cavitation could be the occlusion of an arteriole by a viable mass of tumor cells. Next the vessel wall is invaded and invasion of the perivascular space. The lung architecture is destroyed with a central avascular necrosis. When the tumor breaks in the alveoli, a communication ensues between its semi-liquid contents and the respiratory passage below the bronchial level. The epithelium will keratinize and respiratory motion will aid stripping of the dehydrated stratified material from the cavity wall. Aside of thrombosis the wall of the cavity is lined by tumor cells. Only in a few cases clear necrosis is responsible for the cavitation.

Symptoms

Although at the current time the diagnosis of lung metastases is usually made before symptomatology occurs, by staging and routine imaging methods, it is interes-ting to see how in the pre-CT era the diagnosis was obtained. As can be expected, the progressive decrease of respiratory surface and/or volume will lead to dyspnea as the major symptom.

Table 1.7 - Pulmonary Metastases (*)
Symptomatology (N=172) Data of Minor 1950

Sign		Sign	
Cough	73.3%	Weakness	8.5%
Dyspnea	42.6	Fatigue	7.5
Sputum	40.7	Anorexia	5.8
Pleuritic pain	29.6	Night sweats	2.3
Hemoptysis	26.7	Tissue expectorate	2.3
Wheezing	3.4	Cyanosis	1.7
Weight loss	8.7	Osteoarthropath	0.6
Fever	8.5		

(*) patients with pleural or bronchial metastases are probably included.

However, the presence of some 'irritation' makes cough a major symptom. Some other symptoms are probably related to more advanced stages. In the series on surgical resection of lung metastases currently reported, the clinical symptomatology is indeed never reported.

We give here the data from a series of 172 patients published in 1950 (Minor). Systemic symptoms in the absence of any pulmonary symptoms have lead to the diagnosis (table 1.7).

Imaging

Common chest radiography will be usually the first imaging method leading to its diagnosis. The radiographic pattern has been described many times (table 1.8).

The advent of computer tomography has revolutionized the diagnosis of lung metastases. It soon become evident that many more metastases could be detected than was supposed by plain radiographs. Plain chest radiography was previously supplemented by whole lung tomography, but in the last decades by CT. The introduction of whole lung tomography allowed the detection of a higher number of parenchymal lung metastases.When computer tomography was available, the number of detected nodules 'increased again'.

As metastases can present either as a solitary (coin lesion) nodule or as multiple nodules, each study has its own probability of metastases detection. Moreover literature studies on these situations must be reconsidered if they concern first diagnosis in a general population or on oncology-patients with a known extrapulmonary tumoral process.

Table 1.8 - Metastases in the Pulmonary Parenchyma
Radiographic pattern in different tumor settings
Modified from Whitesell et al.

Pattern	Common histology, site or setting
Multiple nodules	
Calcified	Osteogenic sarcoma,chondrosarcoma, rarely thyroid, ovary, breast, (post-chemotherapy)
Miliary	Thyroid, renal, ovaries, melanoma
'Cannonball'	Sarcoma, melanoma,rectocolon, kidney
Slow-growing	Thyroid, salivary (adenoid cystic)
Cavitating	Squamous cell carcinoma, most adenocarcinoma, melanoma, sarcoma, germ cell, bladder (transitional)
Poorly defined	Choriocarcinoma, liposarcoma, larynx pancreas, (post-chemotherapy)
Solitary nodules	Non-specific

A coin lesion in the general population can fortunately mean several pathologies other than malignant as several reviews and classical textbooks mention and list. When this population is examined further with pathology obtained by biopsy or thoracotomy, a bronchogenic carcinoma is found in about one third, a metastasis from a (known) tumoral process in 10% and a benign disease in about half of the patients (table 1.9) (Toomes et al.). A similar repartition is found in several published series (not shown).

Cahan et al. have proposed the following empyrical guidelines:

- If the primary malignancy was an epidermoid carcinoma, the new nodule is most likely to be a new bronchogenic carcinoma;
- if the primary was an adenocarcinoma, the new nodule has an equal chance to be a new bronchogenic carcinoma or a metastatic adenocarcinoma;
- if the first primary was a melanoma or sarcoma, the nodule is most likely to be metastatic.

The repartition of the size of the coin lesion between the different pathologies is shown in figure 1.2. There is no significant difference, allowing a diagnosis on size alone.

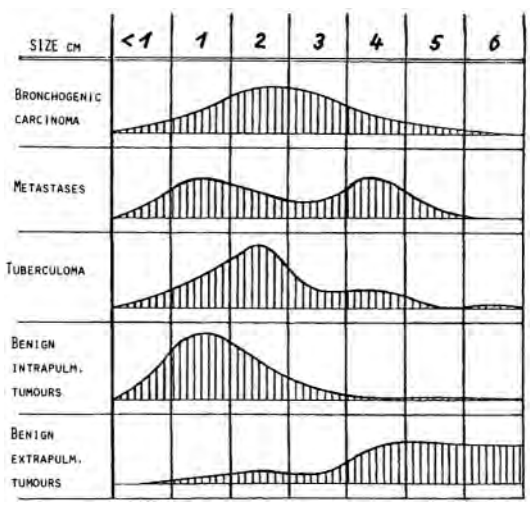

Fig.1.2 - Correlation of size of the coin lesion and histologic diagnosis (N= 955) from Toomes et al., with permission

Table 1.9 - Pulmonary Coin Lesions
Nature as disclosed by histology (N=955)
Data from Toomes et al.

Malignant (N=469)		Benign (N=489)	
Bronchog. carc.	38.1%	Tumors	13.8%
Metastases	9.2%	Tuberculosis	23.6%
Others	1.8%	Others	13.5%

The probability of a coin lesion in a patient with a known cancer to be a metastatic process is of course much higher, but is indeed not 100%, as many nodules will still be benign. In 100 lungs undergoing resection for 273 nodules in 84 patients with a previously treated malignancy, 87% were malignant, 9% benign and even 9 or 4% were found to be a 'new' bronchogenic carcinoma. Of the resected nodules, 27% were not seen on CT, demonstrating the still high incidence of false-negative rate of CT, but the authors did not specify the pathology of these nodules (Peuchot et al.).

Recent studies by Erasmus et al. have concluded that additionally to the radiologic features and the patients' history, growth rate assessment, Bayesian and decision analysis, as well as a pronounced contrast enhancement are all to be included to allow a final diagnosis, but only with a higher not absolute degree of ascertainement. In an extensive study on 141 patients with a solitary pulmonary nodule, malignant neoplasms were enhanced statistically significantly more than benign lesions. At a threshold of 20HU, a sensitivity of 98%, a specificity of 73% and an accuracy of 85%, a prevalence of 49% malignant lesions is obtained. The diagnosis was pathologically confirmed in all cases (Swensen et al.).

The recent introduction of FDG (fluoro-deoxy-glucose-F18)-PET[1]-scan is certainly an important gain to the imaging arsenal, with a high sensitivity, specificity and accuracy in the diagnosis of benign nodules. The use of FDG-PET alone has been reported as a very good predictor of malignancy, better than standard clinical and morphologic criteria used in Bayesian analysis (Gupta et al.).
Comparing Bayesian analysis with FDG-PET scan, Dewan et al. found that as a single test, the latter was more accurate than the standard criteria in correctly classifying nodules as malignant or benign.
There is no doubt that for the detection of metastatic nodules, CT is superior to conventional chest radiography and linear tomography. The problem is the specificity due to the fact that several detected nodules are benign.
CT often provides diagnostic information not available on conventional radiographic studies. Metastatic pulmonary nodules tend to be sharply marginated, while benign nodules rather have irregular margins, perinodular fibrosis, satellite nodules and adjacent pleural thickening. Density is in most cases not helpful in the diagnosis (Sones et al). The higher overall sensitivity of CT over conventional radiography is due to several factors (Davis) (table 1.10).
A major factor is the absence of superimposition of bony thoracic structures and the higher contrast obtained between soft tissue and air-containing lung. Furthermore, the lesions lying close to the heart, the superior sulci, and in the subpleural zone, are so much better visualized, while they occur mostly in the periphery. Not to forget is the continuing technological improvement parallelling the reports with progressively higher detection data. The resolution also permits the detection of much smaller nodules.

In spite of the progress, false negative results have been described. These are due to technical problems inherent to the computation, such as partial volume averaging, respiratory motion artefact and varying degree of inspiration, a problem more frequently encountered in children. Another problem is the differentiation of nodules from 'vessels seen at the end'. Finally, entities such as parenchymal infiltrations, atelectasis, post-operative or post-radio-therapy-fibrosis or pleural effusions can obscure the nodules.

[1] PET: Positron Emission Tomography

Table 1.10 - Pulmonary Nodules
Features helping in differentiating between malignant and benign lesions
Modified from Davis

Morphology :
small (<2cm) metastases are more spherical
large are more polymorphous and irregular
Size: solitary small are more frequently benign
malignant nature increases with size
Clinical factors:
underlying cancer :
H&N: bronchial primary most probable
sarcoma or melanoma: metastases probable
other : both possible
CT attenuation value
Calcified (see table 1.3)
Low attenuation (-8 to 15.5 HU):
observed in testicular malignancies
Bullae : sarcoma
Cavitation : sarcoma, epidermoid, chemotherapy
Vessel entering medial aspect of discrete nodule: metastases very probable

After a study of 193 lung nodules, Furuya et al. were able to delineate some correlations between the type of margin characteristics with the inflammatory or malignant nature of the lesion (fig. 1.3). The study is somewhat biased as there were 113 primary cancers and only 15 metastatic cases. Nevertheless, it was observed that half of the metastatic lesions had typical expansive growth.

CT is also superior for endobronchial lesions. MRI is inferior for this pathology. Another aspect of the superiority of CT is its characterization of lymphangitis and of the parenchymal lung metastases. A number of features can help in the differential diagnosis between benign and malignant lesions (table 1.9 - 1.10).

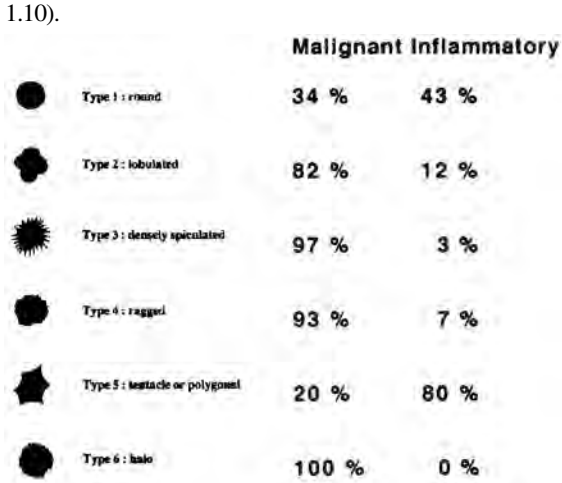

Fig.1.3 - The six types of margin characteristics of a coin lesion with its probablity of malignancy (Furuya et al, with permission)

Diagnosis

As radiologic chest images, with an additional CT, are usually informative, it can been seen from the series described that many nodules are benign, so that in some cases additional cytology or biopsy might be indicated.
Bronchoscopy is usually thought unnecessary, but the report of Poe et al. is very indicative of its limits, outlined in a study of 102 patients. As most pulmonary parenchymal metastases are located in the periphery, many will not be within reach or visible with the fiberscope. The highest yield of tissue confir-mation was obtained for diffuse interstitial disease.

Fiberoptic bronchoscopy was frequently diagnostic in colorectal cancer because this cancer is commonly associated with metastatic involvement of the central airways. In renal cancer, the yield is much lower, because it usually metastasizes in the form of peripheral pulmonary nodules.
The safety, the high yield of information in several suspicious situations and the high yield of diagnostic confirmation makes bronchoscopy an extremely valuable tool in the work-up of oncology patients with suspicious lung findings on chest radiographs or CT.

CT-guided FNAC and/or biopsy is undoubtedly indicated as the diagnostic measure in dubious presentation but also at presentation of solitary or even muultiple lesions. In experienced hands, it has a high accuracy and is very rewarding in the definite diagnostic work-up.

The Primaries of a Coin Lesion

Almost never addressed, although sometimes succinctly, are the data on the primary involved in solitary or coin pulmonary lesion. We found a report dating back from 1978 by Cahan et al. based on surgery (biopsy or resection) or autopsy in 196 cases (table 1.11).

Table 1.11 - Solitary Pulmonary 'Coin' Lesion
Primary involved (N= 196)
Data of Cahan et al. 1978

SupraDiaphragmatic		InfraDiaphragmatic	
Head and Neck	10	Colon Rectum	22
Thymus	1	Kidney	9
Breast	23	Testis	12
Bronchus	4	Urin.Bladder	3
		Cervix uteri	4
Systemic		Wilms'tumor	8
Skin Melanoma	29	Ovary	3
Soft-tissue	37	Myometrium	7
Bone tumors	20	Cervix Uteri	4
Lymphoma	2	Unknown	1

REVEALING or Type 1 METASTASES

Several authors have reported on the wrong diagnosis made of bronchogenic carcinoma in patients presenting with a pulmonary malignancy on chest radiographs. A review of the pathology disclosed another primary metastasized to the lungs. On the other hand, several patients presented with a metastatic nodule from an hitherto unknown primary, in fact the same problem as mentioned.

We mention here some specific results of studies with lung metastases from unknown primary, or type 1 metastases as we call them (see introduction).
In a series reported on 113 patients with pulmonary metastases, 13 had no diagnosis of a primary before thoracotomy (Hutchison et al.). It concerned mainly GIT tumors(4), 2 from the pancreas and the kidney, and 5 from others.
Shepherd had 14 such patients in a series of 104 metastatic lungs, the majority also from GIT (stomach, colon), kidneys and prostatic cancers and from various others.
The presentation of a 'pulmonary' metastasis from unknown primaries was 39% of 404 metastases (Didolkar et al.) and 18% in 302 (Chevalier et al.). Both series admit that the primary was found in only 30% of the cases, inclusive autopsy studies. Pancreatic tumors seem the most frequent primary concerned.

Lepidic Growth

Aside from the pulmonary metastatic types discussed, the lepidic type or spread into the lung along the alveolar walls, in a fashion similar to bronchioloalveolar carcinoma, has rarely been reported. This was first raised by Herbut in 1946. Similar reports followed. They are also called air-space metastases. Tumor cells line or fill alveoli similar to that seen in exudative pneumonia.
The image-presentation concerns air space nodules, pulmonary consolidation, an 'angiogram' sign and nodules with halo-sign, like descibed in the bronchiolo-alveolar carcinoma.
An autopsy series of 416 patients of whom 215 had lung metastases disclosed 34 cases with bronchioloalveolar metastatic type, overall 15.8% of the lung metastases (Rosenblatt et al.1967). The incidence was the highest in kidney cancer and pancreas, both 27%. As stated by these authors, the mimicking with bronchiolo-alveolar cancer is due to

1. malignant permeation of pleural lymphatics with infiltration of the lung by way of the interlobar septa;
2. malignant invasion of the peribronchial lymphatics;
3. nodular and diffuse parenchymal lesions within the alveolar spaces packed with malignant cells.

Reviewing 65 consecutive patients with pulmonary metastases, Gaeta et al. found lepidic growth in 6 or 10% (1996). These concerned a pancreatic carcinoma in 3, a colonic in 2 and 1 jejunal. In one patient, it was a type 1-presentation. Reviewing the literature, they found two series with analogous distribution of primaries, or 27% pancreatic cancers.

Pulmonary Metastases in Children

The clinical aspect is not different from that in adults, but the primaries concern the usual pediatric tumors such as osteogenic sarcoma and Wilms' tumor, the other being much less frequent.

LYMPHANGITIC CARCINOMATOSIS of the LUNG

Lymphangitic carcinomatosa (LC) is a relatively uncommon disorder characterized by diffuse permeation of the pulmonary lymphatics with metastatic cancer cells. It is commonly a late and distressing manifestation of a malignant process with a dismal prognosis. It has been described very early in the literature. Andral (1829), Virchow (1855) and Wagner (1863) were among the first.

Incidence

It is certain that not all cases are reported in the literature. Only small series or some case reports have been published, except those for breast cancer.
Reviewing the literature from 1935 up to 1972, Yang et al. found 275 cases (table 1.12). We are not aware of a more recent compilation.
It seems overall very common in adenocarcinoma, in younger people and in women.
Half of the cases concern stomachal cancers. As mediastinal nodes are rarely described for this cancer, it is obvious that the pathway of spread must be different.
In a series of 203 consecutive autopsies of oncology patients, Soares et al. disclosed lymphangitis carcinomatosa in 36 or 17.7% of the patients. However, they give no specific details on the primary concerned in these patients.

Table 1.12 - Lymphangitis Carcinomatosa
Literature data compiled by Yang 1972 (N=275)

Stomach	122 (44.3%)	Biliary tract	2 cases
Bronchus	62 (22.5%)	Ovary	2
Breast	25 (9.0%)	Nasopharynx	2
Pancreas	14 (5.0%)	Tonsils	1
Uterus	11 (4.0%)	Tongue	1
Colon-Rectum	10 (3.6%)	Esophagus	1
Prostate	10 (3.6%)	Thyroid	1
Kidney	4 (1.4%)	Others	7

Pathways

Several mechanisms have been proposed.
1. In most cases it appears to be the result of an initial hematogenous dissemination. Emboli are lodged in the capillary bed and subsequently invade peripheral lymphatics coursing to the hili. On the radiography, there is no evidence of enlarged hilar nodes.
2. Retrograde dissemination through lymphatic channels in the presence of obstruction within involved broncho-mediastinal nodes.
3. Direct invasion of diaphragmatic pleural lymphatics as has been proposed and appears to be common in stomachal cancers (Filderman et al.).

Pathology

The hallmark of pulmonary lymphangitic carcinomatosa is the presence of tumoral thrombi in the lymphatic vessels of the bronchovascular bundles, the interlobar septa and within the pleura. Localized plaques of subpleural tumors are a very common feature.
It is now commonly accepted that LC results from blood-borne metastases to the pulmonary micro-vasculature, with subsequent spread to the lymphatic channels.

Symptoms

Dry cough accompanied by more or less severe dyspnea is the most frequent symptom and probably occur in more than 60% of the cases. Rarely hemoptysis, thoracal or pleural pain, cyanosis and subfebrility is the first sign. In many patients, the tentative diagnosis of refractory asthma and left heart decompensation was poned.
At auscultation, some wheezing and/or bronchial souffle can be heard. At percussion no apparent sign can be found, except in the rare case complicated with pleural fluid.
Pulmonary function tests show decrease of diffusing capacity, vital capacity, residual lung volume, total lung capacity and lung compliance.
A very rare symptom in pulmonary metastases is bronchorrhea, defined as an excessive (more than 100 ml a day) secretion of mucus. We found three cases reported in the literature: One revealing case for a colonic cancer (Shimura et al.), one pancreatic cancer (Lembo et al.) and recently from a cervical adenocarcinoma (Epaulard et al.). The produced mucus can be explained as a faculty of the metastatic cells having retained their mucus-producing capacity.

Imaging Diagnosis

Diffusely metastasizing tumors present a difficult diagnostic problem, particularly in patients without a known primary cancer.
Chest radiograph shows reticular or reticulonodular infiltrates with the so-called Kerley A and B lines. Associated findings can be hilar enlargment and pleural fluid (fig. 1.4).
The lymphangitic pattern is most likely the result of hematogenous dissemination. LC is characterized by reticulonodular opacities often accompanied by septal (Kerley) lines. Hilar opacities and pleural effusion may or may not be present.

Although the diagnosis can largely be made with common chest radiography, CT is superior in its assessment, mainly because chest radiography can be completely silent in a large part of the patients: up to

50% of the proven cases (Trapnell).

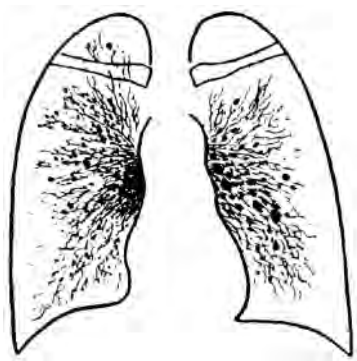

Fig. 1.4 - Typical radiology of lymphangitis carcinomatosa

There is indeed a characteristic pattern especially evident when high resolution CT is used. It consists of
- circumferentially thickened and irregular or nodular ('beaded') bronchovascular bundles;
- multiple linear densities forming a reticular network;
- presence of well-defined polygonal lines;
- discrete lung nodules are uncommon.

It is the combination of these features that makes the diagnosis of LC highly suggestive (Munk et al.).
Pulmonary perfusion scan may be normal, but when positive, the perfusion defects are smaller and more numerous than in pulmonary thrombo-embolism. Tumor micro-embolism is probably the cause of the defect rather than the lymphangitic obstruction.
Pathology studies have resulted in several explanations are at hand of the radiologic abnormalities of the broncho-vascular bundles (Munk et al.):

1. distention of lymphatic channels behind central tumoral emboli;
2. interstitial pulmonary edema secondary to lymphatic tumor obstruction;
3. presence of tumor within interstitium;
4. fibrotic reaction of the interstitium reactive to long standing edema;
5. actual filled lymphatics.

Fibrosis is likely common in breast and bronchus cancer, as both are known for their desmoplastic reaction. This process also needs time. Stein et al. described additional features such as increased thickness of the limbs of the peripheral arcades, diffuse increase in the central linear structures, thickened and irregular fissures.

Although imaging can be very characteristic and almost diagnostic, confirmation should be obtained by transbronchial biopsy. When more localized, as will occur in half of the cases, CT can guide the biopsy needle.

In their landmark publication, Yang et al. proposed four different roentgenological patterns. As type III and IV were found only in bronchogenic carcinoma, we reproduce here only type I and II (fig. 1.5). Type I is a micronodular pattern evenly distributed over both fields, while II has additional hilar infiltration.
Type I was described by Yang only in stomach cancer patients, while type II was present in some cases of stomach cancer and in all other - cervix, breast, thyroid, prostate, pancreas and nasopharynx - except bronchogenic carcinoma.

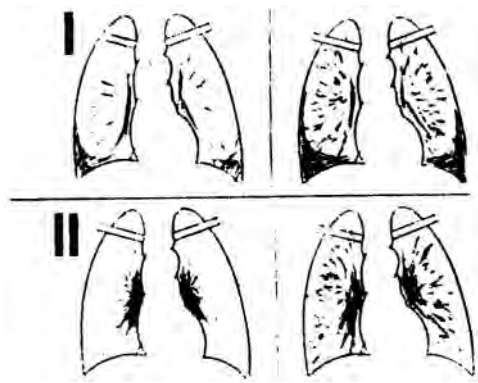

Fig. 1.5 - Types of Lymphangitis carcinomatosa as defined by Yang et al. I: evenly distributed; II extend progressively from hilus to parenchyme. At left, the early stage,; at right, the late stage.

Differential Diagnosis

Radiation damage, opportunistic infections, interstitial pulmonary edema and cytotoxic pulmonary reactions can all occur in cancer patients.
When the diagnosis is not evident at once, transbronchial biopsy remains the diagnostic procedure of choice. In 'difficult' cases, pulmonary microvascular cytology is obtained from blood sample collected using the pulmonary artery flotation catheter of Swan and Ganz. Masson et al., who devised the method, could obtain a confirmatory cytology in all cases.

PULMONARY ARTERIAL TUMOR EMBOLISM

Hematogenously spreading tumor cells from the venous circulation will pass through the right heart in the pulmonary system. The site where they will lodge in the lung depends more on the size of the 'embol'. As has been outlined above, solitary cells will reach the peripheral pulmonary arterial system and eventually give rise to parenchymal metastases.
Cellular aggregates such as microscopic tumorlets will lodge within the same system but more in the larger vessels, and corresponding to their size.
When the number of these embols is large and results in a real 'shower' of tumorlets, a clinical situation of pulmonary embolism can ensue, in the extreme case even to sudden death. This has led Shriner et al. to distinguish between microscopic embolism involving the small arteries, arterioles and the capillaries of the

alveolar septa, and distinct from large tumor emboli causing acute cor pulmonale.

Incidence

In 1457 autopsies of oncology patients, excluding those with bronchogenic carcinoma, arterial tumoral embolism was found in 148 or 10%. In 31 of these (22%) it was the cause of death. Other studies have reported similar incidence rates (Chomette et al.).

Some primary tumors are more inclined to favor this metastatic type such as liver and pancreas, but it can occur in every other cancer. Several case reports have been published concerning one or two cases from various primaries. Several had a fatal issue, surprising the emergency doctors by their absence of reponse to current resuscitation measures.
Reviewing the literature in 1991, Shriner et al. noted that of the 21 cases reported with large emboli, 67% were breast cancer. In the earlier series of Chomette et al. breast cancer was concerned in only 7.4% (table 1.13). Reviewing the literature and adding 6 own cases, He et al. were able to find 39 cases (table 1.14).

Table 1.13 - Pulmonary Arterial Tumor Embolism
Primary Tumor concerned (N=148)
modified from Chomette et al. 1980

Primary	N at autopsy	% ofP(')	% of E(")
Hepatocellular	124	33%	27.7%
Choriocarcinoma	4	25	
Endocrine tumor	41(°)	19	5.4
Biliary tract	51	17.6	6.0
Kidney	51	15.6	5.4
Sarcoma	30	13	2.7
Pancreas	162	11.7	12.8
Breast	113	9.7	7.4
Other(*)	881	5.6	31.7
Total	1457	148 - 10%	100

(') percent of primary; (") percent of all patients with embols; (°) 35 thyroid tumors; (*) conc.12 different.

Table 1.14 - Pulmonary Tumoral Embolism
Cases with subacute Cor Pulmonale
Literature review by He et al. 1989

Stomach	12	Liver	2
Breast	5	Esophagus	1
Choriocarcinoma	4	Colon	1
Uterine Cervix	3	Chordoma	1
Prostate	4	Unknown	3
Bronchus	3		

An extensive literature review was made by Shields et al. in 1992, disclosing 157 cases (table 1.15). The data shed another light on the preponderance of breast cancer.

Symptoms

The symptomatology will range from a mild acute cough to extreme dyspnea and severe respiratory distress with pulmonary hypertension. Pleuritic chest pain, hemoptyisi, fatigue and weight loss are also observed. Physical examination typically reveals signs of pulmonary hypertension and right-sided ventricular overload (Rossi et al.). Death can occur within a few hours and without the correct diagnosis if the patient is unknown to have a previously treated cancer.

Table 1.15 - Pulmonary Tumoral Embolism
Primary Tumors Involved (N= 157)
Literature review by Shields et al. 1992

Breast cancer	40 - 25%
Stomach cancers	22 - 14
Choriocarcinoma	20 - 13
Hepatocellular carcinoma	17 - 11
Bronchial cancer (')	15 - 10
Prostate cancer	9 - 6
Cervix Uteri	7 - 4
Various other	27 - 17

(') the cases with probable coexistent obstructive pulmonary disease or pneumonia were excluded

The clinical distress syndrome does usually not correspond to the abnormalities on chest radiography.
A clinical situation of hypoxemia with clear lung fields is the typical presentation of large embols. ECG is also non-specific, but right ventricular systolic pressure typically exceeds 50 to 60 mmHg (Shriner et al.).
Two groups are distinguished by Kane et al. as far as presentation concerns. Group I are those presenting with a clinically unexplained dyspnea. This worsens progressively with chest pain and chest radiology will show no evidence of any metastatic tumor. Group II patients have no dyspnea at all and apparently died of other oncologic problems. They collected 16 cases from the files of the hospital (table 1.16).
The most obvious symptoms in the series of Shields et al. were shortness of breath in 60% and dyspnea at exertion(40%). Fatigue was reported in half of the patients while non-productive cough only in 20% and pleuritic chest pain in 15%. This correlates with the gradation of involvement of the lung (see further).

Table 1.16 - Pulmonary Arterial Tumor Embolism
Associated Primary Tumor
Data of Kane et al.1975

Group I With dyspnea		Group II No dyspnea at presentation	
Breast	3 cases	Breast	1 case
Stomach	2	Prostate	2
Prostate	2	Liver	2
Liver	1	Pancreas	1
		Unknown	2

Pathology

Four basic different types of tumoral involvement of the pulmonary vessels have been distinguished:

1. large tumor emboli occluding either the main pulmonary arteries or the large segmental branches;
2. generalized lymphatic involvement;

3. pure microscopic tumor emboli involving the small arteries or arterioles and
4. a combination of all three.

Type 1 will result in acute cor pulmonale, while types 2 and 3 both can produce the clinical picture of subacute cor pulmonale. This is characterized as already described by progressive severe dyspnea, signs of right heart failure without previously known cardiac or pulmonary pathology. Type 2 obviously results in a chest radiology with interstitial infiltrate, paralleling lymphangitis carcinomatosa. Type 3 is associated with clear pulmonary radiology (Kane et al.).They collected 44 cases from the literature. Breast cancer seems to be a leading cause (table 1.17).

Table 1.17 - Pulmonary Arterial Tumor Embolism
Primary Tumor for type 3
Literature review by Kane et al.1975

Breast	8	Liver	4
Stomach	6	Choriocarcinoma	3
Colon-rectum	6	Ovary	3
Choriocarcinoma	6	Urinary Bladder	1
Cervix Uteri	5	Gallbladder	1
Skin	1		

As far back as 1903, Schmidt mentioned that in one third of the patients with abdominal mali-gnancy, there were multiple small tumor emboli to the lung. He remarked that the further the embol was organized, the fewer tumor cels it contained.

Chomette et al. distinguish two anatomical types of these tumoral emboli. First, a pure hematogenous, occuring in the typically hematogenously spreading cancers such as liver and kidney cancers. It occurs in early stages but can be dramatic.

The other type is a mixed one, where the arterial emboli are associated with lymphangitis, occuring at a more evoluate and late stages.

Defined as the presence of isolated cells or clusters of tumor cells within the pulmonary arterial system, including the alveolar septal capillaries, arterial tumor embolism can be divided into two modifications as seen at histopathology.

First, intravascular changes with a continuum from frank predominant thrombosis to predominantly tumor emboli. This reflects subacute or progressive 'showering' with tumor emboli from any primary. This leads to obstruction of the smallest vessels that become irritated intraluminally, resulting in intramural changes that can only be visible when the process is not 'too rapid'. Intimal proliferation will enhance the vascular obstruction and result in an additional feature leading to final complete pulmonary vascular obstruction (Bassiri et al.). Alveolar septal embolism should occur in about 10% of oncology-patients at autopsy, but gene-rally in association with the involvement of arterial or lymphatic vessels (Soares et al.). Most probably, this must be what vonHerbay et al. called pulmonary thrombotic microangiopathy observed in 21 patients in 630 consecutive autopsies.

Table 1.18 - Pulmonary Tumoral Embolism
Symptoms and Pathology (N=19)
Data of Soares et al.

Symptomatology	
Dyspnea	57.9%
Respiratory distress causing death	52.6%
Cough	26.3%
Right ventricular failure	15.8%
Cyanosis	21.1%
Peripheral edema	21.1%
Jugular engorgement	5.3%
Pathology	
Right ventricular hypertrophy	42.1%
Right ventricular dilatation	26.3%
Pulm.vascular sclerosis	63.2%
Pulm.hemorrhagic infarct	26.3%
Pulmonary metastases	63.2%

Reviewing 222 consecutive autopsies, Soares et al. found arterial embolism in 19 cases or 8.5% and carcinomatous lymphangitis in 19.8%. Clinically, no difference was observed between both metastatic types. At morphology, right ventricular hypertrophy and dilatation was observed in case of arterial embolism, but also histological signs of pulmonary hypertension and hemorrhagic infarcts. This is different from the lym-phangitis. The cause of death is the pulmonary end-arteritis and modification of the endothelium caused by the arrest of tumor emboli (table 1.18).

Two types of metastatic pattern can be seen at histology (autopsy) (Chomette et al.). The rarest form is the presence of nodular herds within the stroma or within the alveolar cavities (cancerous alveolitis). Most frequent is the presence of neoplastic lymphangitis along the bronchi, the lobular septa and small arteries. At autopsy, thrombosis is invariably found in the peripheral venous system.

In the autopsy study, three subgroups could be identified at autopsy by Shields et al. This parallelels the extent of involvement of the lung by the embolization.

1. patients with predominantly neoplastic microemboli;
2. patients with mixed neoplastic and thrombotic emboli;
3. patients with both neoplastic microemboli and large fatal tumor emboli.

Moores et al. distinguish five patterns:

1. pure tumor embolization of the pulmonary arteries and arterioles;
2. pulmonary intravascular tumor emboli with thrombo-endarteritis;
3. pulmonary intravascular tumor emboli with fibro-obliterative endarteritis;
4. pulmonary perivascular lymphangitis carcinomatosis with arteriolar compression;
5. pulmonary lymphangitis carcinomatosis with necrosis of carcinoma cells and calcification.

Reviewing 1411 oncology-autopsies, Goldhaber et al.

found 56 patients with solid tumors and a major thrombotic pulmonary embolism and 17 with major tumor embolism. The last was defined as

1. more than 15 tumor emboli in muscular vessels, up to 500 μm;
2. more than five tumor emboli in elastic arteries, greater than 500 μm, or
3. at least one tumor embolus in a segmental or larger artery.

Based on the small number of patients, it would appear that half of the patients with tumor embolism had either a bronchial or breast cancer and no GIT tumors, while half of the patients with the thrombotic embolism had breast, bronchial or GIT cancers.

Correct diagnosis was obtained in half of the patient with pulmonary embolism, but only in one of the patients with tumor emboli. Symptomatology was not very different between both groups, although arrhytmia occurred more frequently in the pure embolism group and cough and pneumonia in the tumor group. The conclusion is that, at least in an oncology patient, the symptoms should make one suspect a tumor embolism or even after a certain age, when a neoplasm is unknown in his history. The type of the primary involved does not indicate a real difference, but GIT cancers have proportionally more thrombotic events.

Type 1 Presentation

Margolis et al. reported one case of post-mortem diagnosis in a patient presenting with acute symptoms of dyspnea, progressive cough and tachycardia. Further explorations and imaging pointed to multiple pulmonary embolism not responding to treatment. Autopsy revealed no gross thrombi, but microscopic examination showed occlusion of about 75% of the small arterioles and large capillaries in both lungs. Adenocarcinoma was also found in several cervical and paratracheal nodes, but no primary tumor was discovered. This should make one to suspect a cancer in patients with the clinical presentation of any acute pulmonary embolism.

In a review of 1069 autopsies, Veinot et al. observed three cases who died of subacute cor pulmonale due to tumor embolization from a cancer of the breast, the bronchus and the ovary. In the latter two, the cancer was unknown before death.

Diagnosis

The clinical presentation is completely aspecific, with as mean feauture the initial discrepancy between the symptomatology and the chest X-rays. Reviewing the several reported cases, Bassiri et al. have summarized the features, but not a single one pointed more towards pulmonary arterial tumor embolism than any other pulmonary pathology (table 1.19).

Table 1. 19 - Pulmonary Tumoral Embolism
Clinical Features
Literature Review by Bassiri et al.

Symptoms		Arterial Blood Gas	
Dyspnea	+++	Hypoxemia	+++
Chest pain	++	Respir. Alkalosis	+++
Cough	+	Normal	+
Hemoptysis	+		
Cardiac arrest	+	ECG	
		Normal	+++
Signs		Nonspecific	+++
Tachypnea	+++	S1Q3	+
Tachycardia	+++		
Accentuated P2	++	Chest X-ray	
Jugular distention	++	Normal	+++
Cyanosis	+	Prom. Pulm. Artery	++
Pleural rub	+	Cardiomegaly	++
Crackles	+	Focal atelectasies	+
Fever	+	Pleural effusion	+
		Bilat. infiltrates	+

(*)+++: common (>50%); ++: less common; + isolated cases

Evolution

In 31 of the 148 (21%) cases reported by Chomette et al., embolism was directly responsible for death. In 24 of them, death was sudden or rapid after the first signs. The main situation is acute cor pulmonale. In the other 7, pulmonary hypertension lasting some days or even weeks led to exitus. There is apparently no correlation with the primary cancer involved.

The subacute time course for microscopic tumor embolism may range from several weeks to months, and lies between that of acute thromboembolism and the insidious duration of idiopathic pulmonary hypertension. Hepatic abnormalities and metastases may be present as source of the microscopic emboli. Patients with large emboli or massive microscopic tumor embolization may be very difficult to distinguish from those with an acute pulmonary thromboembolism (Shriner et al.).

One can conclude that the condition is grave. According to He, the average survival after diagnosis was three months.

The observation that in autopsy series, 2% of the patients have pulmonary emboli and that is observed in 4% of the deaths from breast cancer, suggests that this phenomenon is much more frequent than commonly accepted and diagnosed (He et al.).

Imaging

Chest radiographs may be totally normal if the microembolic pattern predominates.

The chest roentgenographic findings in subacute cor pulmonale due to malignant embolization are variable (He et al.). The paradox is the disparity between the clinical distress and the normal appearing image. The chest roentgenogram is normal in a purely embolic condition or when the histologic changes are primarily intra-arterial. When lymphangitic changes are present,

this will easily be recognized.
When pulmonary hypertension occurs, the major chest radiograph findings are cardiac enlargement, proximal pulmonary artery enlargement, increased vessel tortuosity and pruning of distal pulmonary arteries. The findings can however be absent or minimal (Chakeres et al.).
At CT dilated and beaded peripheral pulmonary arteries may be observed. Bilateral peripheral wedge-shaped opacities, suggestive of pulmonary infarcts can also be seen (Rossi et al.). Pulmonary angiography is usually unrevealing except in some cases.
The clinical presence of peripheral thromboembolism will be an indication for pulmonal perfusion isotope scintigraphy. There will be multiple small subsegmental perfusion defects in a geographic like distribution with a resulting subsegmental contour pattern with visualization of pleural fissure and diminution of the total lung volume. Combined with a ventilation-scan, the tumoral embolic process will yield high-probability scans. Moreover, the tumoral process will yield scintigrams with special characteristics (Crane et al.): the defects are smaller (subsegmental), more numerous, tend to be peripherally located, distributed more or less evenly throughout both lungs and best seen on the posterior oblique views. The same perfusion pattern is however also described in other diffuse pulmonary pathologies, so that the pattern is not specific as has been claimed by some authors. Large defects involving one or more lobes is unusual but described (Moores et al.).
In order to confirm the diagnosis tissue should be obtained by open-lung or transthoracal needle biopsy. Others have placed a catheter in the pulmonary artery and obtained blood by slow aspiration from the arterial port.
Some authors have developed cytologic evaluation of pulmonary artery catheter-derived blood specimens. This method can be applied whenever the diagnosis is suspected, based on the relatively acute onset of respiratory distress in an oncology patient. This is indeed an elegant method, but positivity is obtained in only one third (Abati et al.).

Table 1.20 - Mucin Tumor Embolism
Literature review by Kane et al. (1999)

Primary		Embolic Sites
Breast	3 cases	Brain
Bronchus	2	Kidney
Ovary	2	Heart
Pancreas	1	Lung
Cholangiocarc.	1	Spleen

Mucin-Embols

Mucin-embolization has rarely been described in pathology studies of adenocarcinoma patients. This was recently again brought to the attention by Kane et al. reporting on a case of peripheral cholangiocarcinoma. Patient presented with progressive dyspnea and fatigue and a chest radiograph showing multiple patchy and irregular opacities in the periphery of both lungs. Reviewing the literature they found 8 additional cases (table 1.20).
At CT, multiple focal consolidation is seen with surrounding ground glass attenuation in the subpleural space of both lungs. An open biopsy revealed pulmonary infarction caused by intravascular adenocarcinoma, with numerous mucous emboli in pulmonary arteries. There will be no extravascular tumoral proliferation. Indeed, the tumor can only be identified in medium- or small sized muscular arteries and arterioles.
Reviewing the few other published cases, one can state that

- mucin-associated microembolism or thrombosis can show on chest radiography the image of pulmonary embolism, but no infarcts;
- is very rarely detected ante-mortem;
- is very difficult to differentiate from tumor emboli or from tumor associated thromboembolism.

METASTASES to the TRACHEOBRONCHIAL TREE

Microscopic invasion of the bronchial wall is often seen at autopsy and has been reported in 18 to 50% of the patients with known extrathoracic malignancy and/or pulmonary metastases. It originates from adjacent parenchymal metastases or from mediastinal lymph nodes.
Endobronchial metastasis can also be defined as a metastatic lesion of a major bronchus, clinically and radiologically similar to a primary bronchogenic carcinoma (Ikezoe et al.), hence the difficulty of making a definite diagnosis when a primary is unknown.

Incidence

The exact frequency of the different tumors is unknown, but it has repeatedly been reported for breast, colon, rectum and kidney cancers. This type of metastases has also been described in pancreatic and prostatic malignancies, melanomas and some sarcomas.
At autopsy studies in oncology-patients it has been rated to 2% (Braman et al.) or even 25% when histology studies were performed (Rosenblat et al.).
Reviewing 166 consecutive patients with pulmonary metastases from an extrathoracal cancer, Ikezoe et al. found 6 patients or 3.6 % with an endobronchial metastasis.
Compared with parenchymal metastases, they are somewhat rare, but better awareness has led to more frequent diagnosis.
Three reported series allow the calculation of a certain incidence of endobronchial metastases (table1.21). Large bronchoscopy-series report a low incidence.

Metastases within the trachea are much more rarely reported than in the main bronchi. Reviewing the literature, we found that breast, kidney and colon were

the most frequent primaries (table 1.22).

Table 1. 21 - Endobronchial Metastases
Incidence Data from literature

Pisch 1993	39 patients: 32 primary bronchial 7 metastatic (22%)
Cavaliere '96	2008 bronchoscopies (oncologic) (*) 1839 primary bronchial 130 metastatic (6.4%) 69 rare and unusual
Ormerod '98	3353 bronchoscopic (all oncologic?)(*) 1391 visible lesions with 1059 positive histology 16 were metastatic (1.5% of positives) (8 bronchial carcinoids)

(*) number of patients

Table 1.22 - Metastases to the Trachea
Primary Tumors from Literature Review

Breast	4 cases	Testis, thyroid, melanoma,
Colon	4cases	ovary, endometrium,
Kidney	3 cases	esophagus each one case.
Cervix Uteri	2 cases	

Metastases in the main bronchi, or endobronchial metastases are much more frequent. It is thus strange that a review of the literature shows that, initially most were from kidney carcinomas. In the last decades however, several reports have appeared on breast cancers, either specifically or in the larger series (table 1.23). In the series of Cavaliere et al. comprising 130 patients, a large number of thyroid and esophageal cancers are included, most probably by contiguous invasion.

Table 1.23 - Endobronchial Metastases
Primary Tumors from a literature review by the author

Breast	61 cases	Ovary	3cases
Kidney	31	Testis	3cases
Colon	30	Adrenal,pancreas,	
Uterus	13	Head-neck	6 cases
Bladder	4	Prostate, stomach, liver,	
Sarcoma	8	Larynx,Parotid each 1 case	
Thyroid	5		
Melanoma	4		

Table 1. 24 - Endobronchial Metastases
Recurrence interval (N=37)
Data of Quantrill et al.2000

Primary	N	Interval (Mean-Range)
Breast	8	80 (9-222 months)
Rectum Colon	8	44 (0-99)
Esophagus	6	40 (11-88)
Kidney	5	79 (12-159)
Cervix uteri	2	23 (18-29)

One case of stomach (revealing), urinary bladder, melanoma (after 44yrs!), thyroid, endometrium, Ewing, pleomorph adenoma, Hodgkin

Pathology

A series of 37 patients was recently reported by Quantrill et al. They included a number of esophageal cancers included, probably contiguous invasion. They examined a number of features such as the interval depending on the primary cancer (table 1.24) and the site of the metastasis (table 1.25).

Table 1.25 - Endobronchial Metastases
Bronchus involved (N=37)
Data of Quantrill et al.2000

Trachea	4	Le.main bronchus	8
Ri. main/interm	19	Le.lower lobe	4
Ri..lower lobe	7	Le.upper lobe	4
Ri. middle lobe	3	Lingula	1
Ri. upper lobe	6	Bilateral	7

The high incidence at the right main bronchus suggets a correlation with a mediastinal node lying behind this bronchus, or with the esophageal primary? One case with a pedunculated metastasis has been reported in the trachea, 6 years after nephrec-tomy for a renal cell carcinoma (MacMahon et al.).

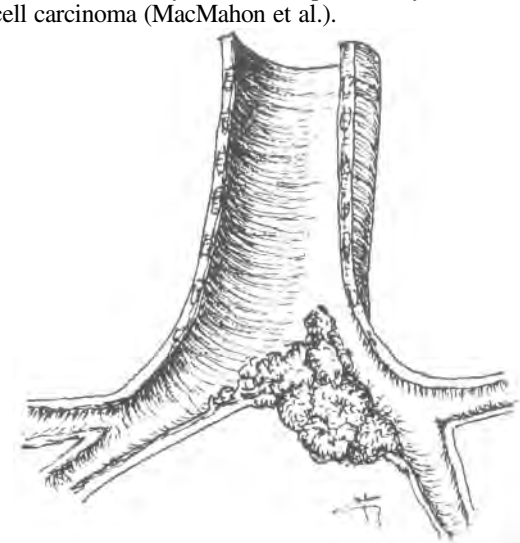

Fig.1. 6 - Pathologists view of bronchial invasion

Reviewing the literature on endobronchial metastases from sarcoma, Akiba et al. found only 17 cases reported. There were 7 cases of leiomyosarcoma of the uterus. The other cases varied (table 1.26).

Table 1.26 - Endobronchial Metastases from Sarcoma
Literature review by Akiba et al. 1994

Uterus Leiomyosarcoma	7 cases
Forearm Leiomyosarcoma	1
Angiosarcoma (arm, unknown)	2
Fibrosarcoma scrotum, leg)	2
Osteogenic sarcoma (bone, uterus)	2
Pelvic Chondrosarcoma	1
Mouth Schwannoma	1
Chest Undifferentiated	1

In a series of 90 'surgical' patients (in evaluation for surgery) bronchoscopy showed invasion of the bronchi in 25 patients or 28%. These findings, reported in 1982, already suggest that bronchial metastases are more common than generally suspected or supposed (Shepherd).

Pathways

Possible routes of tracheobronchial metastases are

1. a parenchymal mass with direct extension into the bronchi or trachea. Invasion of thyroid tumors is common in the subglottis and/or larynx;
2. secondary bronchial extension from involved mediastinal lymph nodes;
3. direct hematogenous spread;
4. retrograde from lymphangitic involvement;
5. dissemination through the bronchial arteries.

Based on these different developmental possibilities, Kiryu et al. have recently proposed a classification system:

Type I.: direct metastasis to the bronchus;
Type II: bronchial invasion by a parenchymal lesion;
Type III: bronchial invasion by a mediastinal or hilar lymph node metastasis;
Type IV: a peripheral lesion extending along the proximal bronchus.

Their small number (38) of patients did not allow to corelate type with type of primary, but they observed that 20/25 were at the right side.

Interval

One remarkable feature is the large spread in the interval time observed (table 1.24). In 16 of 25 patients, the diagnosis was made within 4 years after diagnosis. In the other 9, it was as much as 10 or more years (Shepherd). Large intervals have been reported in the several other case reports.
According to the literature review by Hermann et al., the endobronchial metastases were revealing the primary in 15 patients of whom 8 renal cancers. The others were 2 thyroid cancers, 2 adrenals, 1 from a testicular, a pancreatic and a prostatic tumor.

Symptoms

This type of metastatic involvement results in respiratory signs or symptoms in only a small fraction of the patients, with probably less than 5% of the patients dying from a solid tumor.
The symptomatology, when present, consists of cough, hemoptysis, wheezing and dyspnea as would be expected. Hoarseness and stridor are present in more advanced cases. It very rarely preceeds the first diagnosis.

A dreaded complication is the plug-in embol of a tumoral piece within the large bronchus. This occurred in a patient after biopsy of a metastases in the right stem bronchus from a pelvic chondrosarcoma. (Schenk et al.).

Diagnosis Imaging

It is obvious that bronchoscopy plays an important role in diagnosis, and is the method of choice. An intra-luminal mass, a polypoid lesion, a diffuse tumor involvement with ulceration and eventually narrowing of the bronchus are the main features observed, either alone or combined. Granular mucosal involvement with nodular protrusion can also be observed.

Typical radiographic findings may show partial obstruction with expiratory air trapping evolving to complete obstruction, later complicated with atelectasis or retro-obstructive pneumonia. At chest radiography, Ikezoe et al. discern three patterns: 1. lobar or segmental atelectasis or obstructive pneumonia, 2. a pulmonary nodular mass with hilar node involvement, 3. a mediastinal mass.
In many case reports, CT was the main imaging confirming the metastatic location. The obstruction and/or narrowing of the bronchus can be readily demonstrated, as well as the mediastinal mass and the segmental or lobar atelectasis.
An additional CT of the neck and mediastinum is necessary to assess its status. An esophagoscopy can be necessary to evaluate the region posterior to the trachea.

Table 1.27 - Endobronchial Metastases
Relevance of bronchoscopy depending on primary
Data of Poe et al.

Primary	N	positive - %
Breast	58	33 - 57%
Colon-rectum	14	11 - 79%
Genito-urinary	9	3 - 33%
Others(')	24	13 - 54%
Total	105 (")	60 - 57%

(') summarized from the original report; (") procedures

Table 1.28 - Endobronchial Metastases
Relevance of Bronchoscopy according to Clinics
Modified from Poe et al.

	N(')	positive - %
Sign		
Cough	61	38 - 62%
Hemoptysis	9	8 - 89%
Local wheeze - rhonchi	10	8 - 80%
Other	41	19 - 80%
Radiology		
Solitary-multiple nodule	24	12 - 50%
Localized infiltrate	24	13 - 54%
Atelectasis	28	19 - 68%
Diffuse interst.disease	19	13 - 68%
Hilar-Mediastin.enlargm.	10	3 - 30%

(') number of procedures

There is only one study, dating back to 1985, on the effectiveness of bronchoscopy in these patients (Poe et

al.). They studied the incidence according to the primary involved and to the first clinical sign or symptom (table 1.27 and 28).
In patients with a known or unknown tumor, presenting with an abnormal or suspicious radiograph, the yield of the bronchoscopy was very high. In 33 procedures an endobronchial lesions was visible and in 27 others the diagnosis of metastases was obtained by additional bioptic or cytologic procedures. Furthermore, any clinical sign was highly related to the positivity of the procedure.

Differential Diagnosis

When the symptomatology first presents in a patient without a known primary (type 1), confusion with a primary bronchial (tracheal) carcinoma is possible. This masquerade has been reported in several publications. Present day immuno-histochemistry is of great help in identifying a specific histology type.
When an endobronchial tumor is found at bronchoscopy, the diagnosis of metastasis should be considered when (Hermann et al.).

- the patient has been treated for a cancer of the breast, the kidney and the recto-colon;
- the patient is a non-smoker;
- the patient is female;
- on chest X-rays, nodular lesions are found as well as metastases in other organs.

METASTASES to the PLEURA

A distinction should be made between two types of involvement: firstly, tumoral nodules spread over the pleural surface and secondly there is the malignant pleural effusion. In most cases a mixed picture is observed, at least in epithelial tumors. Sarcomas usual present only with tumoral involvement.
Pleural effusion is a common complication of several neoplastic diseases. Its incidence also largely depends on the type of primary. The majority come from bronchial cancer, breast cancer and lymphomas.

Incidence

Pleural metastases, with or without effusion, develop in about 3% of patients with gastric, breast and ovarian tumors. Seven to 15% of the bronchogenic carcinoma develop pleural effusion (Fenton et al.).
About 50% of the cancer patients with disseminated disease will sooner or later present a pleural effusion.

The tumors mentioned in table 1.29 account together for about 80% of all malignant pleural effusions. As far as pleural effusion is concerned, 40 to 50% of them are encountered in oncology patients (Review by Filderman et al.).

Table 1.29 - Pleural Metastatic Effusion
Repartition according to Primary type
Modified from Filderman et al.

Primary	N	% in evolution
Bronchus	641	36%
Breast	449	25%
Lymphoma	187	10
Ovary	88	5
Stomach	42	2
Primary Unknown	129	7

Table 1.30 - Pleural Metastatic Effusion
Primary Neoplasm as cause (N= 472)
Data of Johnston,1985

Male Patients (N=285)		Female Patients (N=187)	
Bronchus	49.1%	Breast	37.4%
Lymphoma	21.1	Genital tract	20.3
G I Tract	7.0	Bronchus	15.0
Genito Urinary	6.0	Lymphoma	8.0
Melanoma	1.4	G I Tract	4.3
Mesothelioma	1.0	Melanoma	3.2
Various	3.5	Urinary tract	1.1
Unknown	10.9	Various	1.6
		Unknown	9.1

Table- 1.30 - Pleural Metastatic Effusion
Primary Neoplasm as cause (N= 3811)
Data of Hsu et al. 1987

Male Patients (N=303)		Female Patients (N=482)	
Bronchus	61.7%	Bronchus	46.2%
G I Tract	11.8	G I Tract	6.6
Lymphoma	10.5	Lymphoma	4.9
Urin.tract	1.6	Breast	20.7
Upper resp.tract	1.6	Genital (*)	13.2
Thyroid	(1)	Thyroid	(1)
Other	(8)	Other	(2)
Unknown	9.6	Unknown	7.4

(*) 64 cases, of whom 41 from ovaries

As should be expected in for every type of metastases, there is a definite difference in the primary causing the pleural problem. The reports, however, never make thois distincytion. An exception are the reports by Johnston (table 1.30) and by Hsu et al. (table 1.31).
Over a period of 13 years, 5888 pleural fluid specimens were submitted, of which 10% (584 from 472 patients) were malignant at cytological diagnosis.
Bronchial cancer and lymphoma occur in 70% of the male patients, while breast and genital cancer occur in 60% of the female patients.
The series of Hsu et al. contains many more female patients. A literature review by Fenton et al. resulted in interesting data both on the incidence of effusion for any cancer and on the proportion of all instances of effusion (table 1.32).

Pleural metastases occur relatively rarely in other primaries, but it has been described in almost all, even for brain tumors. The high number and proportion in both gender for bronchial cancers should be noticed, certainly in progression in female patients in the last

decades. Another feature is the high number of unknown primaries at presentation in both series. During follow-up most of them seem to be bronchial.

Table 1. 32 - Pleural Metastatic Effusion
Literature Review by Fenton et al.

	Proportion of all Effusions	Probability of Developing
Bronchial Cancer	17-55%	7-15%
Breast cancer	15-40%	3-5%
Ovarian cancer	6-17%	3%
GIT, usually stomach	3-6%	4%
Lymphomas	6-17%	25%

The autopsy data of Rodriguez-Panadero et al., reporting separate data between pleural metastases and pleural effusion are also intersting. They found in 191 oncology patients, or 22% of all autopsied, 107 cases with some pleural metastases. No breast cancer was included, as autopsy was not performed in patients with an obvious diagnosis (table 1.33).

Table 1.33 - Pleural Metastatic Effusion
Pathology at autopsy (N=191)
Data of Rodriguez-Pandero et al.1989

Primaries	N	Pleural Metastases	Pleural Effusion
Bronchus	39	24	15
Lymphoma	28	7	5
Other	129	38	8
Sarcoma	3	3	1
Other	3	3	1
Total	202	75	30

The reported data are not accurately detailed. Pleural involvement was observed in 55 of the 191 cases, and malignant effusions were found in 30 of the 55 cases or 15% of all patients. Reviewing their data, however 75 with pleural metastases and 30 with effusion can be counted. The data show that there are apparently more patients with pleural (solid) metastases than with effusion, at least at autopsy of these selected patients.

Etiology - Pathogenesis

Several mechanisms can explain the genesis of pleural metastases.
Metastatic involvement of the pleura can be caused by
1. Direct contiguous invasion from a pulmonary or chest wall tumor;
2. Hematogenous embolisation from any tumor;
3. Transdiaphragmatic and transserosal from an abdominal neoplasm.

Chernow et al. distinguish five different mechanisms that can cause pleural effusion
1. Direct involvement of the pleura by tumor;
2. Lymphatic or venous mediastinal obstruction;
3. Endobronchial obstruction;
4. Postobstructive pneumonitis with a parapneumonic effusion;
5. Severe hypoproteinemia.

Impaired lymphatic drainage of the pleural space seems the predominant mechanism responsible for an effusion.
Pleural fluid is normally removed by stomal connections between pleural space and the lumen of the lymphatics of the parietal pleura. Such lumina are present with a density of about 1 per mm^2 and are localized in the lower mediastinum, the intercostal space of the lower thorax and on the diaphragmatic surface. The stomata connect the pleural space with the submesothelial lymphatics.
The lymphatics of the pleural space drain into the anterior, middle and posterior mediastinal lymph nodes but also to the intercostal and the sternal lymph nodes.

Interference of the flow can thus occur anywhere between the stomata and the mediastinal nodes. The most frequent reason is, however, the neoplastic involvement of the mediastinal nodes, resulting in an obstruction of the efferent flow from the pleural space, leading to an accumulation of fluid within the pleural space.
Another cause is the neoplastic involvement of the pleura leading to an obstruction of the stomata, so that pleural fluid will accumulate. The presence of a tumor will lead to reactive changes in the pleura with shedding of mesothelial cells, and thickening of the mesothelium and of the pleura.
- The pleural invasion can also lead to an increased permeability of the microvasculature, with an increase in fluid production.
- Bloody malignant effusion is caused by direct tumoral invasion of blood vessels, occlusion of venules and/or capillary dilatation of vasoactive substances.

Peritoneal carcinomatosis of any cause tends also to propagate either by lymphatics either by subserosal spread to the superior mediastinal nodes, causing pleural effusion by lymphatic obstruction.
Malignant thymoma develop in the mediastinum, but many come in touch with the pleura and have a high propensity to disseminate within it.

Pathology

Every clinician has remarked that the involved pleural side does not always correspond with the side of the primary. Data on the respective distribution are nonexistant in the literature, with the exception of a small series reported by Chernow et al. (table 1.34).

In spite of the small number, the data indicate that there are proportionally more bilateral effusions in breast cancer: 11 of the 17 patients. In bronchial cancer only 5 of the 29 patients are similarly affected. An ipsilateral effusion is indeed the rule in bronchial cancer, while patients with other cancers may have

effusion on any either both sides. The amount of fluid is very variable and does not correlate with the extent of intra-thoracal metastases (table 1.35).

Table 1.34 - Pleural Metastases
Location compared with side of primary
Data of Chernow et al.1977

Primary	N	Pleural Cavity Right	Bilat.	Left
Bronchus R.	17	15	2	0
Bronchus L.	12	1	3	8
Breast R.	10	3	5	2
Breast L.	7	0	6	1
Ovary R.	1	1	0	0
Ovary L.	4	1	2	1
Stomach	5	2	1	2

Table 1.35 - Malignant Pleural Effusion
Size (volume of fluid) (N=93*)
Data of Chernow

<500mL	9.7%
500-1000 mL	31.2
>1000mL, not massive	46.2
Massive	12.9

(*)Lung infiltrates were present in 40%, pulmonary or mediastinal metastases present in 31%

The effusion is in approximately one-third bilateral and in one third unilateral on either side (Chernow et al.). Interesting data were provided by Boutin et al. They performed thoracoscopy in 215 of 1000 patients with chronic effusion and previously negative investigations, however very suspicious for a malignant process.
Of them, 150 cancers were diagnosed, 115 with metastatic effusion at biopsy and 35 with mesothelioma, the latter explained by nearby asbestos industry. The macroscopic findings are illustrative for the variable aspect of the pleural metastases (table 1.36). Data on the primaries are however not reported.

In a prospective study in 208 cases by Loddenkemper et al., a diagnostic sensitivity of 95% was obtained, while fluid cytology was positive in 62% and a needle biopsy only in 44%.

Table 1.36 - Pleural Metastases
Macroscopic findings at thoracoscopy (N=150)
Data of Boutin et al. 1981

Nodules or masses anywhere in cavity	56
Pleural thickening with positive biopsy	39
Mixed aspect, sessile masses or nodules of cancerous large thick plaques	32
Lymphangitis of the pleura	7
Non-specific changes	16

From autopsy data, it is clear that both visceral and parietal surfaces are usually involved when bronchial cancer infiltrates the pleura. Neoplastic cells do indeed seem to spread across the cavity to the parietal blade.
Malignant pleural fluid may be serous, serosanguinous or bloody. A serous effusion is probably paramalignant, but can be malignant too.
The already mentioned literature review by Fenton et al. provided interesting data (table 1.37).

A bloody (hemorrhagic) malignant effusion suggests pleural metastases and can result either from direct invasion of blood vessels, occlusion of venules, tumor-induced angiogenesis or increased tumoral capillary permeability (Sahn).
Turbid effusion suggests also paramalignant effusion mostly secondary to bronchial obstruction.
Post-mortem studies have provided much information. Visceral involvement is obvious for bronchial cancer, but it must occur either from contiguous invasion, or through pulmonary artery invasion and embolization. This can also explain, at least partly, the effusion accompanying peripheral parenchymal metastases.

Table 1.37 - Malignant Pleural Effusion
Pathology Charateristics
Literature Review by Fenton et al.

Red cell count >100.000	33%
Exudative (*)	85-95%
Low glucose (compared w.serum)	33%
Low pH-level	50%
Cytology positive at first specimen	50-66%
Cytology positive in 3 samples	69%
Cytology positive or suspicious	70-80%
Positive pleural biopsy	45%
Positive thoracoscopy	80-97%
Diagnostic cytogenetics	80%

(*) serum protein >0.5 and LDH fluid/serum >0.6

The involvement of parietal pleura can result either from spread of neoplastic cells from bronchial cancer across the pleural cavity, or from secondary implants from floating neoplastic cells. The parietal pleura is of course invaded by tumors of the thoracic wall as most frequently from breast cancer.

Pleural metastases from abdominal tumors result usually as a tertiary step from established liver metastases.
Chylothorax is characterized by milky fluid. Cancer is the most common non-traumatic cause, especially malignant lymphoma. Tumors affecting the thoracic duct or the subclavian vein are also frequent causes. The definite malignant diagnosis must be confirmed to differentiate it from pseudochylous or chyliform effusions.

Interval

The interval between the occurrence of the primary and the diagnosis of a malignant effusion varies according to the type of primary. It averages more than 3 years in breast cancer, malignant melanoma and lymphomas. It is only 1 to 2 years for tumors of the female genital tract and urothelium and is considerably shorter in pulmonary and gastrointestinal cancers. More

data have been provided by VandeMolengraft et al. In 171 patients, the pleural effusion occurred before or at the diagnosis in half of the bronchial cancer patients. The primaries were not given. In the other patients, the interval varied according to the primary (table 1.38). It was much shorter in bronchial cancer than for the other ones, where it amounts 2 to 3 years.

Table 1. 38 - Malignant Pleural Effusions
Interval between first diagnosis and effusion
Data of VandeMolengraft et al.

Primary	Average
Bronchus	3.2 weeks
Breast	143.9
Ovaries	103.8
Lymphoma	100.3

Clinical Manifestation - Symptoms

The most common symptom, in more than 50%, is dyspnea. Chest pain develops in about 25% and can be due to involvement of the chest wall, parietal pleura or the ribs. Nevertheless many patients - 20% - are asymptomatic notwithstanding a large volume present. Other symptoms are mainly caused by the tumor spread (table 1.39).

Table 1.39 - Malignant Pleural Effusion
Clinical manifestations (N=96)
Data of Chernow et al.

Symptom		Clinical Sign	
Dyspnea	57%	Effusion	92%
Cough	43	Adenopathy	21
Chest pain	26	Chest pain	4
Weight loss	32	Clubbing	2
Malaise	22	Pleural rub	2
Anorexia	15	Cyanosis	2
Fever	8	Cachexia	37
Chills	5	Fever	9
No Symptoms	23		

Diagnosis

Clinical examination will find dullness to percussion, decreased fremitus and breath sounds at auscultation and detect effusion in most of the patients (table 1.40). Radiology and thoracocentesis will confirm it.

Table 1.40 - Malignant Pleural Effusion
Diagnostic Possibilities

Clinics (percussion, auscultation)
Fluid evacuation, punction
Fluid Biochemistry
Fluid Tumor Markers
Fluid Cytology
Imaging: Chest radiography
Computer Tomography
Thoracoscopy and Biopsy

Imaging

Standard AP and lateral chest radiography can detect pleural fluid in excess of 175mL (Berkman et al.).
The finding of bilateral effusion and a normal heart size suggests a malignant cause. About half of these patients have a malignant effusion, but other diseases can produce this radiological picture (lupus pleuritis, constrictive pericarditis, rheumatoid pleuresy, cirrhosis and others).
More than l00mL fluid is present in about 60% of the patients and massive effusion in 10%. Fewer than 10% of the patients have evidence of pulmonary metastases on the chest radiograph. Patients with non-bronchogenic carcinomas have a high probability of concomitant liver metastases.

If the mediastinum is not shifted contralaterally with a large effusion (>1500mL), the following diagnoses are probable (Sahn):
- carcinoma of the ipsilateral main stem bronchus resulting in atelectasis;
- a fixed mediastinum with malignant lymph nodes;
- malignant mesothelioma;
- extensive tumor infiltration of the ipsilateral lung mimicking a large effusion.

If the mediastinum is shifted away from the pleural effusion, the most likely diagnosis (Moores) is a disseminated carcinoma of non-thoracic origin, such as the breast or ovary.
If the mediastinum is shifted towards the effusion, carcinoma of the bronchus, with either partial or complete obstruction, is most probable.
In bilateral effusion and normal heart size, malignancy involving the mediastinum is most probable.

Computer tomography is of value in distinguishing between benign and malignant involvement of the pleura. In the presence of a known pulmonary malignancy, pleural and chest wall involvement can accurately be ascertained with CT. Malignancy is almost certain when circumferential pleural thickening, parietal pleural thickening of more than 1cm, nodular infiltration of the pleura or mediastinal pleural involvement are observed.
When an anterior mass is visible together with a uni- or bilateral convex solid pleural mass, it is probably a thymic neoplastic process.

A closed pleural biopsy is indicated in undiagnosed effusion, following fluid analysis when malignancy is suspected. It provides a diagnosis in about half of the patients. It can be obtained under radiologic control. Thoracoscopy or open biopsy with thoracotomy should be reserved for difficult cases

Cytology

Pleural fluid cytology has a positive diagnostic yield in 40 to 90% with a pleural malignancy. In the remai-

ning patients, a second paracentesis, pleural biopsy or thoracoscopy will provide further proof of malignancy. So-called negative cytology effusions are paramalignant effusion, without pleural involvement, but with an indirect cause of fluid effusion.
The cellular contents of malignant pleural fluid have been described by Sahn (table 1.41).

Initial cytology is positive in about 65% of the patients in whom the malignancy of the effusion will be confirmed. A second sample in initially negative cases will yield a positive result in an additional 20%. When the effusion is exudative, a biopsy might be indicated, if needs be, at thoracoscopy. Cytologically negative and false-negative exudates with mesothelial cells but without fibrin and of more than three months duration remain indicative of malignancy, according to a 'rule' of Wihman. This applies for bronchial carcinomas, but also for other carcinomas. Repeated cytology can be useful but rarely add to positivity.

Table 1.41 - Malignant Pleural Effusion
Cellularity Data of Sahn

1. Red cell count usually ranges from 30 to 50,000 cells/mL.
2. The nucleated cells, lymphocytes, macrophages and mesothelial cells account for 1500 to 4000 cells /mL. In about half of the cases of effusion, the lymphocyte predomi-nates (50-70%).
3. Malignant cells can be absent even in clearly pleural metastases, or be the total cellular population.
4. Poly-morpho-nuclear leucocytes account for less than 25%. They sometimes predominate in pleural infection.
5. Eosinophils (>10% of the nucleated cells) are rarely present, only in 5% of the effusions, but are common in bloody effusions.

Combined cytology and biopsy will enhance results but only for a small part (Winkelman et al.).
Several authors however have stressed that only 60% of the malignant pleural effusions is positive at cytology. This has led to the study of other parameters (Miédougé et al.).

Several authors have emphasized that the most common cell-type found at examination are the adenocarcinoma or undifferentiated type. Squamous cell type is relatively uncommon. This last amounts for only 0.6% of the patients in a series reviewed by Smith-Purslow et al. It concerned mainly malignancies of the bronchus, of the female genitalia and even of the larynx. Its rarity compared with the high number of bronchial cancers could be explained by the fact that most cancers do not originate at the periphery close to the pleural blade and further that effusion is mainly the result of obstructive pneumonitis or neoplastic obstruction rather than from shedding of cells in the pleural cavity.

Biochemistry

Classically the effusions are categorized in transudates and exsudates.

Light proposed previously the following criteria for an exsudate:
- pleural fluid/serum protein ratio of more than 0.5;
- pleural fluid/serum ratio lactodehydrogenase of more than 0.6;
- pleural fluid LDH of more than two-thirds the upper normal limit for blood.

Malignant effusions frequently have low values for pH and glucose and elevated LDH.
Later authors proposed a more adequate definition of an exsudative effusion: an albumin gradient of less than 12g/L, the gradient being the serum albumin value minus the pleural fluid albumin. High pleural amylase in a malignant effusion is probably associated with a malignancy of the bronchi, the ovaries and the pancreas (Joseph et al.). It is, however, not indicative of a carcinoma. Amylase can be of importance in the absence of pancreatitis and esophageal rupture. It is more elevated in adenocarcinoma than in mesothelioma.
Pleural fluid determination of CEA, cholesterol, hyaluronic acid and LDH-isoenzymes are of no diagnostic value for malignant effusion (Sahn).

Tumor Markers

Numerous studies have tried to evaluate tumor markers, but more to make a diagnosis of the primary involved whenever the primary was still unknown. We will not review the extensive literature and numerous studies on the subject here. Miédougé et al. evaluated 215 pleural effusions of which 21% were of an unknown primary. They stated that the association CYFRA+NSE+SCC was able to discriminate adenocarcinomas from small cell lung cancers. Associating CEA+Cal5.3+ CYFRA21.1+NSE and SCC, the sensitivity and complementarity of the different markers made the diagnosis possible in 84% of the malignant and cytologically negative effusions, the diagnosis of the type of primary could be made on the basis of the result of the tumor markers.

Type 1-or Revealing Malignant Effusion

This is a well-known situation rarely discussed in the literature. Reviewing 174 pleural malignant effusions in 133 patients, Monte et al. disclosed 18 cases (13.5% of the patients) where it was the first manifestation of a cancer. At final diagnosis, half of them were from a bronchial cancer (table 1.42).

Another large series on cytology of malignant pleural effusion was reported by Sears et al. Of the 592 patients with a positive cytology, the primary was unknown at presentation in 82 or 13.8% of the cases. No epidermoid cancer presented with a malignant effusion

first. After an investigation, the primary remained unknown in 31 patients or 47% (table 1.43). A malignant pleural effusion in a patient without known malignancies is caused in 30 to 50% of the cases by a bronchial cancer.

Table 1. 42 - Type 1-Malignant Pleural Effusion
Series of Monte et al.

Primary	Male	Female
Bronchus Carcinoma	9/18	3/19
Breast cancer	0	0/48
Female Genital Tract	--	2/9
Gastrointestinal Tract	0/4	0/4
Pleura Mesothelioma	1/2	1/2
Miscellaneous	0/5	0/5
Still unknown	2/2	0/1
Lymphomas	0/4	0/3
Whole group	12/35	6/91

Table 1.43 - Malignant Pleural Effusion
Primary unknown at presentation
Data of Sears et al.1987

Adenocarcinoma (N=66)		
Ovary	9	13.6% of adenocarcinomas
Bronchus	23	34.8%
Pancreas	2	
Tuba Fallopii	1	
Not found	31 or 47%	
Non-Epithelial	16	

Table 1.44 - Paramalignant Pleural Effusions
Modified from Filderman et al.

Local Tumor effect	
Lymphatic obstruction	predominant mechanism of fluid accumulation
Bronchial obstruction with pneumonia	para-pneumonic effusion
Bronchial obstruction with atelectasia	transudate, does not rule out operability
Chylothorax	disruption of thoracic duct chyle in pleural space (lymphoma)
Vena Cava Sup.Syndrome	transudate, due to increased systemic venous pressure
Systemic effect of tumor	
Pulmonary embolism	hypercoagulability state
Low plasma oncotic pressure	low serum albumin, anasarca
Treatment	
Radiotherapy	Fibrosis of mediastinum, impairing lymph flow
Drug reactions	
Methotrexate	pleuritis, pleural thickening or effusion
Procarbazine	hypersensitivity reaction
Mitomycin	aggregates of lymphocytes resolves with drug withdrawal
Bleomycin	id. resolves in a few weeks

Differential Diagnosis

Any pleural effusion in a cancer patient does not always mean a malignant process. Aside from benign reasons such as infections and other, several effusions can be labeled paramalignant, as outlined by Sahn et al. (table 1.44). There is no pleural involvement but they can be caused by a local effect of the tumor, by systemic effects of the neoplastic process or by the treatments applied.

Chylothorax

A particular and rather rare type of pleural effusion is chylothorax. It is described as the accumulation of chyle within the pleural cavity. Oncologic causes are common as three quarters of the cases are non-traumatic. Malignant lymphomas are the primary in about 80% of the malignancy associated chylothorax.

Chyle is the lymph of intestinal origin and is typically a thick milky or creamy fluid.
From the bowel mucosa the chyle is transported by the intestinal lymphatics which form progressively larger lymphatic vessels draining to the cisterna. It lies anterior to the first two lumbar vertebrae, between the aorta and right crus of the diaphragm. After ascending through the diaphragm along with the aorta, the thoracic duct comes in the posterior mediastinum right of the midline between the aorta and the azygos vein, crosses the midline between the sixth and fourth thoracic vertebrae behind the esophagus. It continues posterior to the aortic arch over this structure to drain the into the venous system at the supraclavicular fossa (fig. 7.33).
The non-chylous lymph from the left hemithorax drains along the pulmonary and pleural lymphatics forming the left broncho-mediastinal trunk joining the duct when it reach the great veins. From the right hemithorax the lymph drains via the right broncho-mediastinal trunk.

Table 1.45 - Chylothorax in Oncology
Primaries involved - Literature data

Author	Primary	
Roy 1967	Lymphoma	23
	Bronchus	5
	Pancreas, Prostate, Testis	each 1
Graham 1994	Carcinoid of ileocaecal valve	1case
O'Callaghan 1995	Lymphoma 4 cases	
Browse 1997	Lymphoma 6	
	Cervix Uteri cancer	1case
Mares 1998	Lymphoma	18
	CLL (*)	1case
Wallace 2000	Carcinoid of ileum	1case

(*) this patient had also a colon adenocarcinoma, but the presence of metastatic nodes is not stated

There are many anastomoses between the lymph vessels and the between the lymph vessels and veins at the ascending part of the duct and the right posterior intercostal lymphatics, allowing collateral flow and an alternate route in case of thoracic duct obstruction. When these collaterals are defective as through the pre-

sence of malignant lymph nodes, chyle can follow two routes to reflux in the pleural cavity. Retrograde flow from the left posterior lymphatics via the lymphatics of the parietal pleura or via the left broncho-mediastinal trunk to lymphatics of the pulmonary parenchyma and the pleural cavity.
Chylothorax occurs almost exclusively at the left when the duct is obstructed, but right sided will occur when the right thoracic lymphatics are also obstructed (O'Callaghan et al.).

Primaries

The oncologic cause is either an intrathoracic or an infradiaphragmatic cancer metastatic to the mediastinal lymph nodes. Lymphomas are the most frequent and amount to more than 85%. In most reports the side of the chylothorax is not given (table 1.45).

METASTASES to the HEART and PERICARD

It is well known that secondary invasion of the heart occurs 30-40x more frequently than primary tumors of the heart. They are a particular chapter in oncology, due to their long-term elusive nature, but now relatively easily detected with the modern imaging methods.

Pathways

The mode of spread reflects more or less the type of primary involved.
Tumors originating in close proximity to the heart such as bronchial, mammary and esophageal cancers spread by direct extension or through lymphatic spread.
Hematogenous dissemination is the usual mode for all other tumors. Lodging into the myocard through the coronary arteries, the tumor cells can expand and invade the epicard. This can lead to a pericardial effusion.
It would seem that both pericardial sheets have a different lymphatic vascularisation. The lymphatic drainage of the heart consists of an extensive subendocardial plexus, draining through the myocardial channels into the subepicardiac plexus. This connects with the lymphatic plexus of the aortic adventitia, further towards the mediastinal nodes. The epicard or visceral part has an extensively developed network draining towards a node at the base of the heart, connected with mediastinal nodes. The parietal pericard has a poorly developed lymphatic system.

Incidence

Large autopsy statistics report an incidence of 2 to 25% of cardiac metastases. We need to remember that autopsy studies are subject to several biases. The most accurate reports from oncology institutes have high values, around 10%. The incidence also depends on the primary (table 1.46).

Retrograde lymphatic flow from the mediastinum towards the epicard is very frequent in bronchial carcinoma and a late manifestation in breast cancer, mainly metastasizing towards the axillary nodes. Cardiac metastases almost invariably result from retrograde lymphatic extension from malignant para-aortic nodes. Malignant pericardial effusion will be encountered when the mediastinal nodes are invaded (Marek et al.).

Table 1.46 - Cardiac Metastases
Incidence according to primary (Javier et al.1967)

Primary	N	%	with M	N	%
Melanoma	49	46.9%	Esophagus	102	8
Sarcoma	58	15.1	Pancreas	63	6
Bronchus	275	24	Stomach	189	6
Breast	335	18	Head & Neck	327	5
Liver	18	17	Cervix Uteri	259	3
Testis	18	11	Urin.Bladder	147	3
Kidney	49	10	Colon rectum	443	2
Low genit.(*)	39	10	Ovary	60	2

(*) penis, scrotum, vulva

Another type of distribution is found in Eastern patients, according to the report by Lam et al. from Hong Kong (table 1.47). The series reflects, of course, the incidence of the primaries, with many bronchial and esophageal cancers and very few breast cancers.

Table 1.46 - Cardiac Metastases
Involved primaries - Autopsy series (Lam et al. 1993)
N= 12485 autopsies, 154 with cardiac metastases
Data collected 1972-1991

Bronchus	33.1%(*)	Ur.Bladder	2.6%
Esophagus	20.1	Melanoma	2.6
Liver cancer	5.2	Sarcoma	2.6
Breast	3.2	Leuk.Lymph.	16.8
Stomach	3.2	Colon	1.9
Pancreas	2.6	All others	6.1

(*) of all patients with cardiac metastases

The incidence of cardiac metastasis also depends on the presence of other metastases, more specifically of lung metastases. Excluding bronchial cancers, Weiss found an incidence of cardiac metastases of 19% in patients with lung metastases, but only 2.7% when no lung metastases were present. This may be explained by a cell traffic from the lung seedlings. A small proportion of cancer cells are expected to survive the passage through lung capillaries. Similarly, cardiac metastases are much less frequent when the cells have to pass the portal system as is the case with colorectal tumors, resulting in a low incidence.

Pathology

The heart can be involved either in its walls (to make

a distinction between metastases within the pericard, the epicardium, the myocard and the endocard) or within its cavity by tumoral thrombi (fig. 1.7).
Metastases in the myocard are usually embolic via the coronary arteries, rarely by implantation in the right cardiac chambers from cells carried through the venae cavae (table 1.48).
Data on the relative distribution show that myocardial metastases are the most frequent, but pericardial involvement is also common (table 1.49). The reports however, do not always make a distinction between hematogenous and contiguous invasion. There is nevertheless a remarkable difference in the data reported. The relative distribution will also be influenced by the type of primaries, as some invade more through contiguity and others more by hematogenous spread.
The series of Lam et al. show a 60% of the cases with pericard invasion, correlating with the high number of intrathoracal tumors. Of 186 patients with myocardial metastases, there were 133 (71.5%) at the left side.

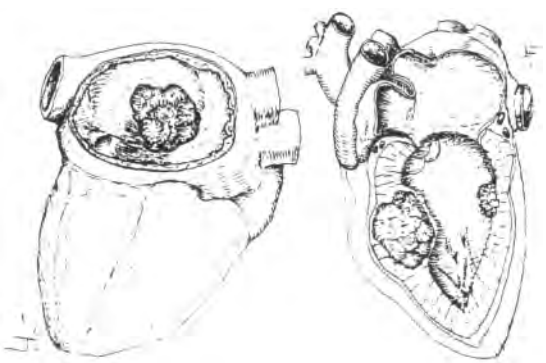

Fig.1.7 - Artist's view of cardiac metastases: left in the atrium, right in the ventricle intra-myocardial and in the epicard

Table 1.48 - Cardiac Metastases
Distribution within the heart
Literature data

Structure	Eschwege 1970	Mukai 1988	Klatt 1990	Abraham 1990
N of autopsies	2258	2649	1095	3314
N with metast.	177	407	110	95
Pericard	38%	19.2%	---	28.4%
Epicard	9	33.4	83%	13.7
Myocard	31	41.5	42	53.9
Endocard	2	5.9	17	3.9
Pancardial	20	---	8	---
Chamber involved		Mukai		
Right only		22.2%		
Left only		32.7		
Septum only		6.0		
Bilateral or Diffuse		34.0		
Intracav.TuThrombus		4.6		

Kaup et al. interprete this as correlating with the relative muscle mass of both ventricles. One could, however, also state that fewer metastatic cells will implant in the right wall, while smaller cell groups will come from the present pulmonary metastases, as stated by Weiss.
Willis states that lymphatic permeation from the epi- and pericardial lymphatic vessels is not rare. Less common is invasion of the venae cavae and pulmonary vein that does not extend further than the atria at death.

Table 1.49 - Cardiac Metastases
Distribution within the Heart according to Primary
Autopsy data (N= 154) by Lam et al. 1993

	Pericard	Myocard	Endocard
Bronchus	43	13	5
Esophagus	21	15	4
Liver	4	3	1
Breast	4	0	0
Stomach	5	1	0
Colon	3	1	1
Pancreas	5	2	1
Ur.Bladder	4	1	1
Thyroid	2	2	1
Melanoma	1	2	4
All patients	113(59%)	55(29%)	24(12%)

Note: tumors with occur in less than 4 cases have been omitted.
Note: several patients had more than 1 location.

Metastases have been described within the sinusal node, the papillary muscles and within the valves.
There is no particular structural preference for the cardiac metastases according to the primary, except that breast cancer has a relatively high incidence of pericardial metastases, probably because of the mechanism outlined above (Eschwege et al.).

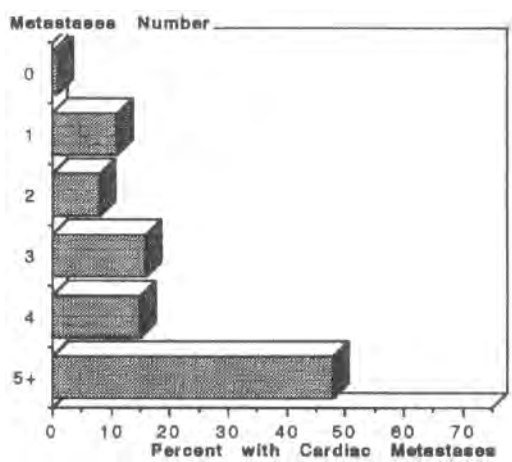

Fig.1.8 -Frequency of cardiac metastases correlating with the number of other intrathoracic metastatic sites. (Redrawn from Kawinski et al.)

There have been several hypothetical explanations for the rarity of cardiac metastases:

1. the vigourous kneading action of the myocardium;
2. the relative avascularity of the endocardium;
3. the peculiar metabolic pathway used by cardiac musculature;
4. the rapidity of blood flow through the heart

chambers;
5. the right angle of the coronary arteries towards the aorta.

It would seem, however, that the low rate of incidence is related to observational practices, especially at autopsy. Furthermore, as Weiss has pointed out, the incidence is not lower when one takes in account the volume of the heart compared with other organs.
An extensive autopsy study performed in 2,833 oncology patients by Karwinski et al. showed that cardiac metastases are almost always accompanied by a large number of other metastases. Unfortunatedly, they did not specify the organ localisation in their report. Intrathoracic metastases or invasion was seen in 63% of the bronchial cancers, but in 81% in other tumors.

Isolated cardiac metastases were seen in only one patient. The number of cardiac metastases increased with the number of other metastases. When the number of metastatic sites increased from 4 to 5, the heart involvement increased fourfold to about 60% (Fig. 1.8).
A number of authors have remarked on the progressive increase of cardiac metastases within the last decades. If longer 'cures' of several cancers obtained can be the reason, it is without doubt that better clinical and especially the application of echocardiography must be the main reason.
Other particular forms of cardiac metastases have been described and will be discussed further.

Pathways of Pericard Metastases

Pericard metastases will originate in a small percentage by hematogenous seeding. The large majority, however, have their origin in any mediastinal, particularly the subcarinal and hilar lymph nodes, from where the dorsal aspect of the pericard sac is invaded. This has been particularly well demonstrated by Tamura et al. for bronchial cancer and is probably applicable to other cancers as well. This is however almost never alluded to in the CT-image of patients with pericardial effusion or tamponade. This is well illustrated in figure 1.9.

The first step is mediastinal involvement, from where tumor cells will retrogradely flow to the lym-phatic channels of the pericard and of the cardiac surface, producing some lymphatic obstructions. This has been studied extensively and microscopically confirmed by Kline.

Symptoms of Cardiac Metastases

Malaret et al. have outlined the signs that could herald the presence of metastatic lesions
1. the sudden appearance of a tachycardia or arythmia;
2. the appearance of a pericarditis;
3. the appearance of congestive heart failure, usually intractable;
4. the appearance of a myocardial infarct.

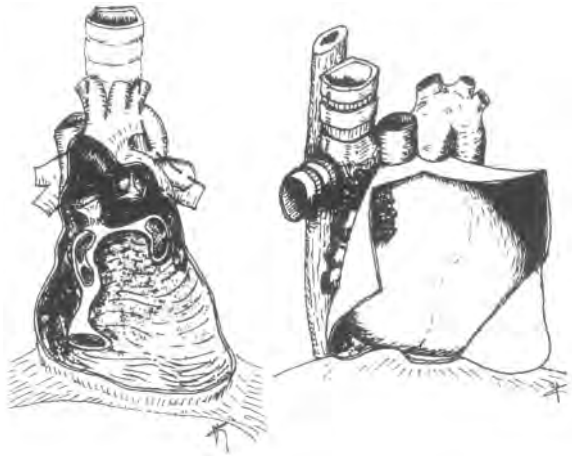

Fig.1.9 - The mechanism of the genesis of malignant pericard invasion

A certain systematization is possible (Stark et al.).
Signs of effusion, constriction, tamponade or pericardial inflammation are present in pericardial metastases. Classically persistent S-T segment elevation, low voltage and/or electrical alternants are associated with this. Myocardial metastases usually present with ectopic electrical activity, tachy-arhythmias and conduction defects, but also with infarct patterns because of the transmural replacement of myocardium by the tumor. Myocardial infarction can result from tumor emboli to the coronary arteries (table 1.50).

Table 1.50 - Cardiac Metastases
Symptomatology classification (Hanfling)

Not suggestive	
	Absence of cardiac symptoms
	Terminal cardiac embarassement
	Congestive heart failures
	Sudden death
	Subacute bacterial endocarditis
Suggestive	
	Heart block
	Symptoms referrable to any location other than a block
	Cardiac dysfunction without apparant cause in patients with cancer
	Accumulation of hemorrhagic pericardial or pleural fluid

Table 1.51 - Cardiac Metastases
Symptomatology in 292 patients (Javier et al.1967)

Asymptomatic	24.3%
Unexplained arrythmia	13.0
Pleural effusion	12.3
Unexpl.grad.congestive fail.	8.5
Mediast.involvement	6.8
Vena Cava Sup.Syndr.	4.4
New unexplain.murmur	4.0
Decreasing heart sound	3.0
Non-specific symptoms(*)	10.2

(*) cough, dyspnea, chest pain.

Endocardial and/or intracavitary involvement will be characterized by obstruction of the ventricular in and outflow. One reason may be a progressive encroachment of the valvular orifices. Mobile and pedunculated tumors will result in valvular regurgitation. Systemic emboli could occur from the intracavitary tumors.

Table 1.52 - Cardiac Metastases
ECG- Symptomatology (N=101)
Data of Javier et al.1967

Normal ECG-	23%
Axis deviation	4
Arrhytmias	44
Conduction defects	9
Low voltage	17
Pericarditis	2

Table1.53 - Cardiac Metastases
ECG- Symptomatology (Hartman et al.,1982)

- Non-specific changes
  - Sinus tachycardia
  - Non-specific ST and T-wave anomalies
  - Low QRS- voltage
  - Premature atrial contractions
  - Premature ventricular contractions
- Conduction system changes
  - Right-bundle branch block
  - Fascicular blocks
  - P-wave changes
  - Paroxysmal atrial flutter, fibrillation
  - Junctional rythm
  - Atrioventricular block
- Myocardial changes
  - Q-waves and ST-segment elevation (persistent)
- Pericardial changes
  - ST segment elevation(transient)
  - Electrical alternans

Endocardial involvement is much less frequently reported than in the other parts. Bryant et al. observed in a description of three cases either pure endocardial or surface involvement, an associated intra-cavitary thrombus because of a surface lesion and one extension from a myocardial metastasis.
Reports on the relative frequency of the symptoms as well as ECG-signs are rare (table1.51, 52 and 53).

Symptoms of Pericard Effusion

The effects of pericardial effusion will depend on the rate of exudation, the elasticity of the pericard, the myocardial mass and the circulating blood volume (Malviya et al.). A slowly accumulated volume can become very large before symptoms occur. This makes the clinical features or symptomatology of cardiac metastases highly variable. It is usually non-specific and will imitate signs and symptoms of any cardiovascular disease. They are only suspicion signs. Most frequent are arythmias, congestive heart failure or cardiac tamponade. There is obviously a correlation with the site of metastases.

The symptoms of pericard metastases in particular do not differ greatly from this. They include impaired coronary circulation, encasement of cardiac innervation, pericarditis, tamponade or a combination of them. Dyspnea and tachycardia are the most frequent presenting symptoms (Wilding et al.).
The best report as far as clinical and radiocardiological aspects is concerned was published by Beretta et al. They studied 21 patients and added 151 from three well-studied series (table 1.54).

Pericard effusion was observed in 65 autopsy-patients. Adenle et al. examined the clinical records of these patients (table 1.55) and observed that the effusion was known or suspected in only 26 patients. Dyspnea and signs of cardiac dysfunction were the main symptoms, while 60% had no relevant symptoms.

Table 1. 54 - Metastases to the Pericard
Clinical, Cardiological and Radiological Features
Data pooled from 4 series as reported by Beretta et al.
N=172 patients(')

Symptoms		ECG-findings	
Dyspnea	86.0%	Low voltage	60.6%
Chest Pain	33.6	Abnormal T-wave	43.6
Orthopnea	25.6	AV-Block	8.4
Asthenia	5.0	Puls.Alternans	8.1
Cough	54.0	Abnormal ST	9.4
Clinical Signs		Atrial Flu-Fibrill.	9.4
Tachycardia	60.7	Bundle block	3.1
Low pressure	39.2	Normal ECG	4.0
Swelling neck vein	52.2		
Peripheral edema	26.5	Radiology	
Fever	14.0	Cardiomegaly	72.5%
Syncope	38.4	Pulmon. changes	35.4
Pericard rub	6.2	Pleural Effus.	48.8
Pulsus Paradoxus	35.7	Cardiac Insuffic.	11.1

(') Thurber et al.1962 (N=55), Shepherd et al.1987 (N=58), Cham et al.1975(N=38), Beretta et al. 1992 (N=21)

Table 1.55 - Metastases to the Pericard
Clinical Status of Autopsy found pericard involvement
Data of Adenle N =65 1982

Sign		Finding	
Dyspnea	20/65	Pleural Effusion	13/65
Tachycardia	7/65	Hepatomegaly	7/65
Pedal Edema	6/65	Cardiomegaly	5/65
Ant. Chest pain	6/65	Ascites	4/65
Jug. vein dist.	5/65	Rales	4/65
Weakness	5/65		

NO SYMPTOMS ante Mortem 39/65 (60%)

Central chest pain mimicking angina can be present with pericarditis. The pain can remain precordial or migrate to the side of the chest. Swallowing pain may be the main presenting sign. Posner et al. stress the importance of chest pain and dyspnea, while cough is quite rare. Facial swelling occurs in malignant pericardial disease (and not with radiation or infectious pericarditis and is associated when present with concurrent vena cava superior syndrome. Several authors have shown that pericardial effusion or metastases are

asymptomatic in about half of the patients (table 1.55). Site and size of the metastases were however not reported, since it is obvious that small metastases can indeed be asymptomatic.
At auscultation, the pericardial rub is pathognomonic, but only present in early development. It has to be distinguished from the pleural rub, while the patient holds his breath.
Many other symptoms have been described, but all are aspecific and non-diagnostic, as they can occur in any cardiac or pericardiac effusion pathology.

Cardiac Tamponade

Constrictive pericarditis occurs when a thickened fibrous pericardium hampers the diastolic filling of the ventricles. When the pressure has increased further, resulting in a decompensated state of the cardiac function, the situation can be termed 'cardiac tamponade'. The severity of the tamponade depends on several factors, such as the rapidity of fluid accumulation, the fluid volume and the tempo of compression of the heart (Theologides). When the fluid accumulation is slow, the pericard can stretch gradually and the heart will gradually tolerate higher degree of compression. The amount can reach 1 to 2 liters in benign condition, but usually less in malignant conditions.
The presence of pericard fluid in an oncology patient is not obligatory malignant. Infectious (viral) processes should be excluded, as well as a sequellar process on previous radiotherapy or even chemotherapy (Pogany et al.). In a series reported by Haskell et al., the tamponade was malignant in only 23 of the 56 (41%) patients.

A pronounced degree of decompensation leads to severe more general symptoms such as extreme anxiety, precordial oppressive feeling, retrosternal pain and pronounced dyspnea. Dysphagia, nausea, vomiting epigastric pain are some of the misleading symptoms. When constriction of the heart is pronounced, the patient can present with a shen face, profuse perspiration, impaired consciousness, mild confusion and even deep coma.
Rapid and laborious breathing, peripheral cyanosis, engorged neck veins and plethoric face are signs of extreme tamponade. Typical, but not specific to the cause, is also the pulsus paradox (Table 1.57).

Cardiac Involvement in Children's Tumors

Information on secondary cardiac involvement in childhood is scanty. It seems lower than in adults because of the absence in children of epithelial cancers and malignant melanoma. Huh et al. reported on 8 cases, with Wilms (2), lymphoma (3) and 1 teratoma, 1 pleuropulmonary blastoma and 1 neuroblastoma

TYPE 1 or REVEALING Metastases
A malignant pericardial effusion is rarely an initial manifestation of malignancy. Fincher has collected 61 cases from the literature from 1974 to 1991.
They can be added to a survey by Fraser, who included 29 cases from 1935 to 1973. We have grouped the primaries concerned on table 1.56. All cases included had a cytological confirmation of malignancy, histologic confirmation or diagnosis inferred following the detection of pericardial tumoral nodules. The presence of bronchial adenocarcinoma as primary in nearly 40% of all cases should be noted.
Another survey was made from 1935 to 1992 by Muir et al. This yielded essentially the same data, but they found additionally 3 cases of pleural mesothelioma and two of ovarian carcinoma.

Table 1.56 - Pericardial Metastases TYPE 1
Literature survey and data by Fincher 1993 (modified) N=90

Bronchus	56 (62.2%)		
Adenocarcinoma	35 (38.8%)	Kidney	2
Squamous cell	12 (13.3%)	Breast	1
All other	9 (10.0%)	Unknown	7
Gastrointestinal	5 (5.5%)	Lymph. Leuk.	12
Pancreas	1	Sarcoma	2
Stomach	1	Thymoma	2
Colon	1	Pheochrom.	1
Unspecified	2	Thyroid	1

Table 1. 57 - Clinical and Graphic Signs of Cardiac Tamponade
Modified from Krisanda

Clinical		Radiography	Electrocardiography	Echocardiography
Rising venous pressure	100%	Enlarged heart shadow	Total electrical alternans	Ri.Ventr. diastolic collapse
Puls Paradoxus >10mmHg	98%	w.normal pulmonary vasc	ST-elevations (pericarditis)	Ri.Atrial collapse
>20 mmHg	77%	Prominence of superior vena cava	Low limb lead voltage	Le.ventr.diast.Coll.
Dyspnea	80%	Pleural effusions	Tachycardia	Pericardial effusion
Tachycardia	77%	Epicardial fat lines on lateral view	Non-specific ST-T changes	Tumor nodules on hear
Hypotension	36%			Congestion of venae cavae (sup.and inf.)
Small, quiet heart	34%			Respirat.variation of dimensions
Pericardial friction Rub	5%			
Elevation of diastolic chamber pressure				
Absent Y-descent with prominent X descent				
Reduced stroke volume and cardiac output				
Elevated intracradial pressure				

In 1998, Islam et al. reported the retrieval of 131 cases between 1935 and 1997. In 39.6%, they concerned a bronchial cancer and in 28% a lymphoma or leukemia. A heart or pericardial malignancy was the primary concerned in 10%. They reported the first case of a renal cell carcinoma presenting with a tamponade.

Imaging

X-ray diagnosis of tumoral involvement of the heart is disappointing. Only an enlarged cardiac sil-houette is reliable for pericard effusion. It has been stated, however, that even up to 200 ml of fluid can result in normal images (Biran et al.).
Intracavitary metastases could be visualized by nuclear cardioangiography but also with plain angiography, holding the danger of a secondary embolisation.
If previously one had to rely on clinical and ECG, the present day method of choice is echocardiography.

It is the best and cheapest screening method and it will reveal the presence, the extent and the complications of the cardiac metastases.

Three types of images have been described (Reynaud et al.).:

1. a well-circumscribed mobile mass within one of the cardiac chambers. A protusion within the valvular ring will cause obstruction and hemodynamic problems. A dilatation of the right chamber(s) is usual;
2. an infiltrating, sessile mass filling one of the chambers;
3. an infiltrating mass resulting in a prominent thickening of the ventricular walls and reaching the pulmonary infundibulum.

It has been definitely established that CT and MRI can show metastases anywhere in the heart. These imaging techniques allow multi-directional slices and also tissue differentiation, more precisely than of echocardiography.

Additionally echocardiography will

1. detect pericardial tumors, such as a small cauliflower-like tumor, with irregular echo with or without some effusion;
2. the myocardial involvement is more difficult to detect, especially when small. The echogenicity of the lesion will differ from the normal myocard, with some heterogenity and deforming of the contours of the epi and endocard. The neighbouring zone can be either hyper or akinetic.
3. the rarer 'pure' endocardial involvement is common in melanoma, but is frequently associated with a thrombus (Brochet et al.).

Pericardial metastases are also well visualized by echocardiography (fig. 1.10), As pericardial effusion grows in size, the following phases can be discerned (Wilding et al.):

1. development of an echo-free space between the right ventricular wall and the chest wall;
2. swinging of the heart in the pericardial sac;
3. abnormal septum motion;
4. late systolic mitral valve prolapse.

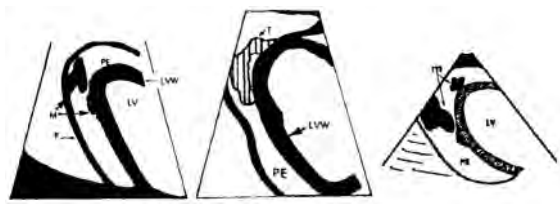

Fig. 1.10 - Cross-sectional echocardiography illustrating some features of pericardial metastatic growth within a pericardial effusion. (from Chandraratna et al.)

Myocardial metastases in the form of malignant infiltrating mass have a peculiar granular texture and always appear always different to normal myocardium (Lestuzzi et al.). The ventricular wall is thicker, an hypo or akinetic at this level. The transmural invasion modifies the epicardial and endocardial contours, allowing differential diagnosis with thrombi.
CT will delineate the status of the heart and of the mediastinum.

Diagnosis

In making the diagnosis, the most important thing is to have an awareness of the possibility of cardiac metastases in a cancer patient. If radiology and ECG have played a minor role previously, two-dimensional echocardiography is the method of choice to reveal any metastasis, its extension and complications.
Pericardial effusion can be evacuated and cytology of the fluid performed. However, not all malignant effusions show malignant cells.
Most of the malignant pericardial effusions are grossly bloody (45%), while in 31% it is serosanguineous and in 24% serous (Malviya et al.).
Initial cytology was negative in 24 of 34 specimens, later corrected to 17 of 45 (38%). Errors were due to scant cellularity and obscuring blood. Results with pericard biopsy were not better (Bardales et al.). Other authors have proposed pericardioscopy and reported the diagnosis of malignancy in patients where cytology and biopsy were negative (Millaire et al.).
Nevertheless, many are still only found at autopsy, because of their silent clinical presentation. Some series have been reported with more prospective diagnosis of cardiac metastases, depending on clinical and ECG abnormalities.
An overview of the clinicopathology of cardiac metastases is shown on table 1.58.
As already mentioned above, not every pericardiac effusion is caused by neoplastic invasion. About 60% of the effusions examined by cytology are non-neoplastic. A differential diagnosis with several other benign pathologies is mandatory. In oncology patients the effusion can also be due to treatment sequellae such as radiotherapy and chemotherapy, and to medi-

Table 1.58 - Overview of Cardiac Metastases
Modified from Hanfling (1960)

	Pericardial	Epicardial -Myocardial	Endocardial
Pathway	Hematogeneous Direct extension	Hematogenous Retrograde lymphatic Spread from myocard and epicardial metast. Retrograde lymphatic spread from tracheal and bronchial lymphatic channels	Direct implantation Extension from myocard Extension from pericard
Symptoms -Signs	None pericarditis Effusion, serous or bloody Constrict.pericarditis	None Changes in rate or rhythm Unexplained .tachycardia Atrial flutter - fibrillation Heart block, compl. or incompl. Atrioventricular rhythm Premature beats ECG-findings Persistent RS-T elevation Persistent T-wave inversion Bundle-branch block Low voltage QRS Sudden death Congestive heart failure Coronary occlusion Angina pectoris	None Murmurs of stenosis Sudden death
Diagnosis	Awareness Examination of pericard fluid ECG Echocardiography	Awareness Unexpl.arrhythmia in cancer patient Unexpl.ECG changes in cancer pat. Echocardiography	Awareness Development of a murmur Murmur changes w. position Echocardiography

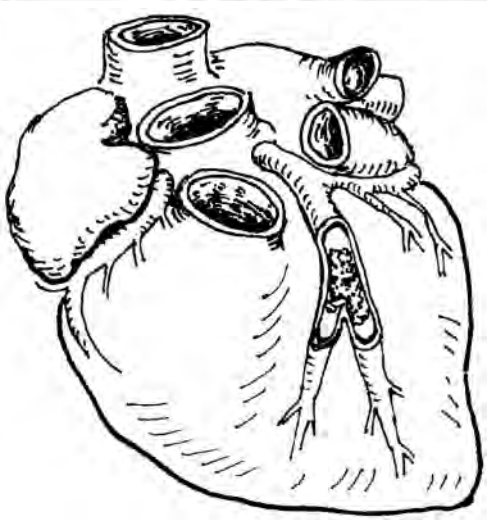

Fig. 1.11 - Artist's view of coronary tumoral emboli

astinal invasion with occlusion of the lymphatics.

Special Situations

Cardiac metastases have been described as occurring with other anatomical presentation and must be mentioned.

Neoplastic Coronary Emboli

Sudden cardiac deaths have been reported in patients in whom at autopsy only malignant neoplastic emboli to the coronary arteries were found (fig. 1.11). Ackerman et al. found 12 reports in the literature, adding two cases. More than half were from bronchial cancers. Neoplastic emboli obstructed the epicardial coronaries in nine and the intramural in three patients. The left coronary system was the site in 83% of the involved vessels. The clinical presentation is commonly a myocardial infarct but as the emboli can be diffuse and small, somewhat aspecific complaints and ECG-signs are common.

A dramatic case was reported in a young woman presenting 1 year after delivery with dyspnea and tachypnea. Six months previously she had chemotherapy for an uterine choriocarcinoma.
At ECG and other investigation it was considered to be ischemic heart disease. At autopsy, however, subepicardial coronary vessels and intramyocardial arteries were completely occluded by metastatic choriocarcinoma (Vasiljevic et al.).

Intra Cardiac Floating Metastases

Echocardiography recognized in the right atrium an intracardiac floating metastasis in a patient treated previously for a testicular tumor. The metastasis was

removed surgically. No such other cases have been reported (Heik et al.).

Intracaval Tumoral Thrombus

A well-known complication of several tumors is the intracaval tumoral thrombus extending into the right atrial chamber or further.
A common occurrence in renal cell carcinoma, this situation has occasionally been reported in other tumors (see part 2).

It occurs in about 20% (8 to 55%) of the renal tumors, involving the heart in 10-50%. Three quarters of intracardiac thrombus occur at the right atrium alone (level IV extension, as defined by Neves et al., fig.1.13).
Exceptionally, it protrudes through the tricuspid valve into the ventricle. A few cases have been reported extending to the pulmonary arteries (Schechter et al.).
Most occur with right-sided tumors, probably due to the complex venous anatomy of the renal region.
There have been reports involving tumors of the testes, the renal pelvis and even renal metastases from a small cell carcinoma (Concepcion et al.). Numerous cases have been reported involving adrenocortical carcinoma (see Chapter 10).

This kind of cardiac involvement must in fact not be regarded as a metastasis, but only as an intracavitary direct extension. The heart itself is not invaded, but its cavity will contain a continuous tumor thrombus extension.

Pathology

A cancerous column within the vena cava invites deposition and agglutination of blood elements on its surface. The ensuing coagulation provides a scaffold for tumor progression, on which cancer cells can multiply. Such a tumor column is polymorphous and friable, with cancer cells enmeshed within a clump of fibrin. One characteristic is that the thrombus does not violate the intima, so that it remains unattached and freely adherent throughout the whole length, except at its origin (fig. 1.12).

The intraluminal thrombus is molded by the tubular contour of the caval vena. It may lose its cylindric shape when the vena becomes fusiformly dilated or otherwise contorted. The architectural form usually persists even when the mass traverses the retrohepatic and intra-thoracic sectors. Higher up the mass is constricted twice at the diaphragm hiatus and at the eustachian valve, making the proximal portion more occlusive. Once the thrombus transgresses to the heart, it is subject to a supplementary set of hemodynamic forces. The thrombus becomes roughly globoid or papilliferous within the atrial cavity.

Pathophysiology

The obstruction or occlusion of the caval vein depends on structural factors such as size, malleability and degree of admixture with blood clot.

Fig.1.12 - Level IV - inferior cava tumor thrombus, extending from the kidney to within the right atrium .

When the inferior caval vein obstructs, several outcomes are possible (Schechter et al.):
- Occlusion of the infrarenal segment is usually innocuous, due to collaterals;
- Occlusion above the hepatic veins produces a uniformly fatal Budd-Chiari syndrome;
- Abrupt occlusion at suprarenal and infrahepatic level has a high mortality;
- Gradual occlusion of the suprarenal infrahepatic, after interruption of the infrarenal segment is well tolerated;
- Gradual occlusion of the suprarenal infrahepatic, followed by right nephrectomy and ligation of the left renal vein at its entrance into the cava, does not entail permanent ill effects;
- Abrupt occlusion of the suprarenal infrahepatic, with concomitant left nephrectomy leads to death from congestion and infarction of the right kidney.

The symptomatology is rather poor. Nephrotic syndrome presents in 20% of the cases with venous extension.
In view of the risks that surgery of renal or other tumors entails, ultrasonography of the vena cava infe-

nor and superior is mandatory in the preoperative setting. CT enhances the possibility of diagnosis especially when intravenous contrast medium is injected. Ultrasonography is a very efficient detection method. The criteria to distinguish them from an acute or a chronic venous thrombosis have been delineated by Bronzi et al. (table 1.59).

Table 1.59 - Neoplastic Venous Thrombus
US. Features outlined by Bronzi et al.

1. The thrombus is always hyperechogenic
2. The thrombus has a dishomogenous texture
3. The thrombus will trend to occupy the lumen completely
4. The vessel is increased in diameter in both directions
5. Venous velocimetry will be reduced or absent
6. Absence of spontaneous pulsatility of the vessel

OUTFLOW TRACT OBSTRUCTION

Metastasis within the right heart leading to right ventricular outflow tract obstruction is another rare condition.
This situation can be encountered

- as primary sarcoma of the pulmonary valve,
- when extrinsic compression occurs,
- as an intracavitary growth of metastatic tumor,
- Rarely when a tumor thrombus transgresses the tricuspid valve

The two last situations should be differentiated from each other, although this is academic and relevant only for the necessary treatment.
Its clinical presentation is characterized by right heart failure, shortness of breath, chest pain and hypotension. At auscultation, systolic ejection murmur can be heard.
An ECG can suggest a right ventricular overload, with small right-axis deviation, right ventricular hypertrophy and right bundle branch block. One should be very careful about the indication of heart catheterization in view of the high risk of further embolization in this situation.
Echocardiography is of course very appropriate and will delineate the extent of the metastases, will assess the functional problem and exclude a pericardial effusion. It can usually also differentiate between an intracavitary metastasis and an extrinsic compression.

Pathology

Because the right heart receives the tumor emboli first, it is obvious that they will either resorb, or embolize further towards the lung, but they can settle and grow further within either right cavity.

Reviewing the literature in 1992, Labib et al. found 11 cases and added three (table 1.60). A striking element was the presence of four colonic tumors, of which two cecal tumors or 4/14 28%. Solitary metastasis was present in 5 of the 10 patients coming to an autopsy and in 2 surgical cases, or overall in 50% of all the cases. It is not impossible that many sudden deaths in known or unknown oncology-patients are due to this event.

Table 1.60 - Cardiac Metastases
Intracavitary metastasis with Right Ventricular outflow tract obstruction - Concerned primaries
Literature review by Labib et al. 1992

Colon (*)	4 (1)(°)	Melanoma	1
Pancreas	1 (1)	Cervix Uteri	1
Breast	1	Ovary	1 (1)
Liposarcoma	1	Kidney	1 (1)
Mal.Fibr Histiocyt.	1	Bronchus	1 (1)
Total	14 (5)		

(*) of which 2 cecum; (°) type 1 metastases.

Another feature is the event as a presentation sign or type 1 metastasis in 5 of these patients. As far as oncologic extrinsic compression is concerned, this will result in a similar outflow obstruction where primary or secondary mediastinal tumors are involved. Up to 1982, 35 cases were reported (Marshall et al.) (table 1.60).

Table 1.61 - Secondary Pulmonary Stenosis
Concerned Primaries
Literature Review Marshall et al. 1982

Lymphoma	3	Teratoma	10
Hodgkin	8	Thymoma	2
Bronchus	4	Sternal tumor	2
Pericard	3	Kidney	1
Lung	1	Unknown Primary	1

Chest pain occurred in 70% with dyspnea in 60%, other symptoms were less common and included cough, palpitations, fatigue and weight loss (10-15%). Murmurs at auscultation led to chest radiograph demonstrating a mediastinal tumor. At auscultation a systolic ejection murmur was found in 90%. If other aspecific features were present on a ECG, it was described as normal in 30%.

TUMOR THROMBUS in LEFT ATRIUM

As with the tumor thrombus extension towards the right atrium, one can extend from the lung itself towards the left atrium, possibly even as far as the mitral valve opening. A left ventricular outflow obstruction is the result, with the constant danger of peripheral tumor emboli, mainly cerebral.
It has been reported in bronchogenic carcinoma of all histologies, but more frequently in pulmonary sarcomas (see part 2), and even metastases from chondrosarcoma in the lungs (table 1.62). It should be mentioned that it concerns almost exclusively left-sided pulmonary tumors as the left pulmonary vein is shorter and closer to the heart. The symptomatology is aspecific and consists of dyspnea, cardiac pain, palpitations and easy fatigability.

The left atrial extension of a tumor thrombus has also been described in relation to pulmonary metastasis from kidney cancers (see chapter 11).

Table 1.62 - Tumor Thrombus Extension in Left Atrium Selective Literature Review

Onuigbo1972	M54	LeUp	Squamous
	M52	LeLo	Oatcell
	M50	LeLo	Squamous
Dore(*) 1988	M60	LeUp	Epidemoid
	M53	LeUp	Large Cell ca
Kodama 1990	M54	LeUp	Large Cell ca
	M67	LeLo	Giant cell ca
	M50	LeLo	Squamous
	M42	RiUp	Adenocarcinoma

(*)Dore mentions 19 pulmonary tumors of which 2 sarcomas and 6 sarcomas with pulmonary metastases (LeUp: Left upper lobe; LeLo:left lower lobe; RiUp: right upper lobe)

Chest radiography will not reveal such problem apart from the pulmonary tumor. Echocardiography is very appropriate as it easily shows the intra-atrial extension.
At CT, various signs indicate the intravascular and intra-cardiac extension (Dore et al.) (table 1.63).

Table 1.63 - Tumor Thrombus Extension in Left Atrium Computer Tomography Signs (Dore et al.)

1. Mass extends into the pulmonary hilus anteriorly
2. Pulmonary vein and its entrance into atrium is not visible
3. Endoatrial filling increases in density with contrast injection
4. Anatomical continuity between lung tumor and atrial thrombus

RIGHT ATRIAL MASS and SEPTUM DEFECT

Obstruction of the tricuspid valve by a right atrial mass in a patient with a right to left atrial septal defect has been reported in a small number of patients with a atrial myxoma. This has been reported in only one patient with metastatic cardiac disease, with a solitary metastatic cardiac lesion from an epidermoid carcinoma of the nasopharynx. The diagnosis of the atrial mass was made by echocardiography, while the patent foramen ovale was suspected as the kidneys were visualized during a pulmonary scan for embols. The tumor was partially resected and the atrial defect closed (Gallerstein et al.).

METASTASES to the THYMUS

Metastases to the thymus are almost not discussed in the literature. One plausible reason for this is firstly the complete absence of any symptom due to its involvement and secondly the difficulty in recognizing thymic structures at autopsy of adults, due to its involution. It has been thought that tumors are unlikely to metastasize in the thymus.
In his classical textbook, Willis mentions one case from a mammary carcinoma, a case of Kaufman from a vulvar carcinoma and the study of Middleton in 1966.

The parenchyma of the thymus has a blood-thymus barrier preventing direct contact with antigens or cancerous cells, possibly preventing the occurence of metastasis (Clark, quoted by Hayashi et al.). Nevertheless the septum of the thymus is comprised of interlobular connective tissue with blood vessels, lymphoducts and nerves, allowing a good possibility of metastasis. The thymus has only efferent lymphatics. All these anatomic factors do not preclude the possibility of metastases in the thymus however (Hayashi et al.).

Incidence

Middleton mentions that finding the thymus at autopsy is difficult. He performed autopsy in 272 patients and could find the thymus only in 167 patients, or 61%. Involvement of the thymus by metastases was found in 25 cases. In 18 cases it concerned a lymphoma, so that 7 of the 102 epithelial had a thymic involvement (table 1.64).

This suggests that thymic metastases are probably not so rare, but they are either not searched for or cannat be found. As we will discuss in the chapter on breast cancer, metastases in the thymus have been described in a substantial number of patients (table 1.65).

Table 1.64 - Metastases to the Thymus Autopsy data of Middleton 1966

Primary	N patients	Metastases
Breast	10	4
Larynx	3	1
Bronchus	18	1
Stomach	15	1
Others	56	0
Total	102	7 (6.4%)

Table 1.65 - Metastases to the Thymus Autopsy data breast cancer

Middleton	1966	4/10 (40%)
Cifuentes	1979	75/707 : 11%
DelaMonte	1984	29/187 : 16%

Although this is a relatively academic problem, data are urgently needed to have better insight into the incidence of these metastases.
We are aware of only one case report where the diagnosis was made during life, after surgical excision of a large (14x9) anterior mediastinal tumor, metastatic from a prostatic carcinoma (Hayashi et al.).

We found mention of metastasis in the thymus of a parasagittal meningioma, discovered at autopsy (Russell et al. in Celli et al.).

One patient was reported presenting with a large thymic tumor, which at histology was found to be a seminoma. Only 10 months later bilateral ovarian tumors were found, previously normal at examination but now causing pelvic pain (Fichet et al.). The thymic metastases (here probably a type 1) can be viewed in relation to the specific evolution of an extra-gonadal germinal tumors.

Symptoms

In the case reported by Hayashi et al., cough and shortness of breath were the symptoms that prompted suspicion, as can be expected from any mediastinal invasion.
There are usually no symptoms, but it is quite possible that some mediastinal 'tumors' go unnoticed or are interpreted in the setting of large and multiple mediastinal nodal metastases.

Imaging

CT is certainly the imaging method of choice, but it is probably not easy to differentiate them from multiple large mediastinal nodes.

METASTASES to the DIAPHRAGM

Studies on metastases in the diaphragm are very rare. This site is often cited as involved in the metasatic pattern associated with ovarian carcinoma and less frequently from other gynecologic tumors.

Incidence

We are aware of only one dedicated report. The figures of an autopsy study by Brennan give an incidence of 12/151 or 7.9%, compared with 3.4% for splenic metastases.
In 198 autopsies of patients with 'soft-tissue' metastases, Rotterdam et al. could detect 68 patients with metastases on either side of the diaphragm.
Metastases at the diaphragm are now being observed in ovarian cancer, in cases of thymic carcinoma and pleural mesothelioma.

Pathways

The undersurface is covered almost entirely by the peritoneum. At the right, it is close to the right kidney and adrenal. At the left, close contact exists with the left liver lobe, the fundus of the stomach, the spleen and left kidney and adrenal. The lymphatics of the diaphragm are in contact with abdominal and thoracal lymphatics by numerous anastomoses.
Like many organs, the diaphragm can be invaded either by contiguity from neighbouring primaries as liver, stomach, pancreas and transverse colon, or through vascular (hematogenous) spread.

Brennan's report however does not distinguish between either modes (table 1.66).
The data are more or less in agreement with present knowledge of the high incidence in ovarian and stomachal cancers, but more data are needed.
Of the 11 patients reported by Brennan - we excluded a reticulosarcoma - 8 were females.

Table 1. 66 - Metastases to the Diaphragm
Autopsy data of Brennan 1971

Primary	N at autopsy	N with metast.	Percent
Bladder	2	1	--
Breast	10	2	20%
Bronchus	48	1	2.0
Colon	13	1	7.1
Ovary	9	3	33.3
Stomach	17	2	11.8
Tongue	1	1	--

Pathology

Of the 11 cases, only two involved the muscle of the diaphragm. In other cases, there was adjacent either peritoneal or pleural involvement. Furthermore many other metastases were present (table 1.67).

Table 1.67 - Metastases to the Diaphragm
Pathology data in 12 patients (Brennan 1971) (*)

Plaques on one or both sites	4
Small nodules on one or both surfaces	2
Direct spread from adj.pleura or lung	3
Involvement of tendineous portion only	1

(*) including one reticulosarcoma.

Table 1.68 -Metastases to the Diaphragm
Autopsy-Pathology (N=61)
Data of Rotterdam et al.1981

Primary	N		Pleural	Periton	Both	Muscle
Supra-Diaphragmatic						
Breast	12/25	8	0	4	8	
Bronchus	8/37	4	0	4	3	
Larynx	1/1	1	0	0	0	
Esophagus	1/3	1	0	0	0	
Infra-Diaphragmatic						
Ovary	20/31	0	10	10	7	
Stomach	6/15	0	2	4	4	
Pancreas	5/17	0	3	2	2	
Colon	5/18	0	4	1	2	
Bile Duct	1/1	0	1	0	0	
Prostate	1/3	0	0	1	0	
Endometrium	1/6	0	0	1	1	
Total	61/137	14	20	27	27	

A very detailed report on diaphragmatic metastases was published by Rotterdam et al., involving 198 patients with soft-tissue metastases, of whom 68 had diaphragmatic metastases. They make a clear distinction between the different surfaces and the muscle, so that in fact only half of them have intra-muscular

metastases (table 1.68). The data clearly show that the pleural surface alone is rarely involved in infradiaphragmatic tumors. All breast cancers invaded the muscle, while the proportion was much lower in ovarian cancer.

Diagnosis

A diagnosis of diaphragm-involvement can be made by CT. Many can be found at staging or debulking surgery for ovarian cancers (see chapter11).
Most cases are still found only at autopsy.

METASTASES to the MEDIASTINAL LYMPH NODES

Metastatic involvement of hilar and mediastinal lymph nodes is much less frequent than parenchymal lung disease, at least in extrathoracic malignancies.
This is mainly seen in genito-urinary tumors as testis. Pancreatic tail tumors, renal, uterine cervix and ovarian carcinomas are also contributors, but this pattern is less frequent than their hematogenous spread.
In about half of these patients, parenchymal lung metastatic disease is also present.

Incidence

A well studied series of metastasis to the mediastinal lymph nodes from extrathoracic neoplasms was reported by MacLoud et al.
Mediastinal nodes are most frequent in renal and testicular tumors. Head and neck cancers accounted however for almost one quarter of the primaries involved (table 1.69).

Table 1.69 - Metastatic Mediastinal Lymph Nodes
Modified from data of MacLoud et al. 1978

Primary	N	Med.Nodes	% of all
Head-Neck	124	4.8%	24.0%
Thyroid	33	6.1%	8.0
Breast	248	1.2	12.0
Melanoma	52	3.8	12.0
Urinary bladder	34	2.9	
Cervix Uteri	18	5.5	
Endometrium	27	3.7	
Kidney	14	21.4	12.0
Ovary	28	3.6	
Testis	17	29.4	20.0
All	595	25(4.2%)	

Table 1.70 - Metastatic Mediastinal Lymph Nodes
Primary Tumor Involved
series of Mahon et al. 1992

Kidney	25	Ovary	3
Testis	7	Stomach	3
RectoColon	6	Bladder	2
Prostate	4		

A remarkable feature is the absence of GIT tumors in this series. However several years later, a small series was reported of 15 cases, involving 9 from a colon cancer, 4 stomach and 2 pancreatic cancers (Libson et al.).

Pathways

Several modes of spread may contribute to intrathoracal adenopathies.
Infradiaphragmatic tumors invade the lymph chain up to within the thoracic duct, with ensuing valvular incompetence with reflux into the bronchopulmonary and mediastinal channels.
The lymphatics from the pelvis and the abdomen drain into the thoracic duct. There is no direct communication between the anterior mediastinum and the duct, which is located in the posterior mediastinum. It is supposed that incompetence or absence of valves could lead to a reflux of tumor emboli from the thoracic duct into the bronchomediastinal trunk. From there, retrograde flow could occur towards the paratracheal, the bronchopulmonary and interlobular lymphatics. At lymphography, mediastinal lymph nodes are visua-lized in about 5-14% of the patients.
A particular spread has been observed in pancreatic tumors, particularly at the tail. Extension occurs through pleural lymphatics into pulmonary connective tissue septa, alveolar spaces and bronchial walls. Further retrograde lymphatic invasion occurs from tracheobronchial or mediastinal lymph nodes.
Direct spread from communicating lymphatics in the neck and axilla results in spread from head and neck cancers and breast tumors. For the head and neck cancers and the thyroid, the drainage is typically first in the neck nodes, distributed between the three chains in the neck: the anterior jugular chain, the posterior or spinal and the transverse or supraclavicular chain. As the anterior chain communicates with the anterior mediastinal, the way for metastatic cells is open.

Table 1. 71 - Metastatic Mediastinal Lymph Nodes
Anatomic Location of involved Nodes (N=50)
Data of Mahon et al. 1992

Anterior Mediastinal Nodes	
Superior Diaphragmatic	4
Internal Mammary	0
Aortopulmonary	25
Right prevascular	12
Middle Mediastinal Nodes	
Subcarinal	31
Right paratracheal	41
Left paratracheal	20
Right hilar	19
Left hilar	10
Posterior Mediastinal Nodes	
Para-esophagal or paravertebral	26

Reporting on 50 patients, of whom 25 had kidney cancers (table 1.70), with mediastinal metastases from infra-diaphragmatic malignancies, Mahon et al. examined the distribution within the mediastinum

(table 1.71).As can be expected, many patients also present with other metastatic sites either nodal as abdominal of supraclavicular. Unfortunately the location was not correlated with the type of primary.

Diagnosis

CT is presently the most adequate imaging method for detecting and delineating the extent of nodal involvement. Histology confirmation can be obtained by transthoracal or transbronchial needle biopsy, mediastinoscopy or thoracoscopy.
Recently, endoscopic biopsy under ultrasonographic control has been added to the methods available. A series of 153 patients submitted to that method was recently reported by Fritscher-Ravens et al. Of the 101 patients without a history of malignancy, a primary bronchial cancer was found in 41, another metastatic cancer in 7, while a benign lesion was diagnosed in the other. In the 52 patients with a known cancer and presenting with mediastinal nodes, metastases were confirmed from 8 abdominal cancers (kidney, stomach, pancreas), 5 bronchial, 2 esophageal, 1 H&N and 3 breast cancers. In 17% of this group, a second primary (mainly a bronchial cancer) was diagnosed.

Superior Vena Cava Syndrome

A vena cava superior syndrome (VCSS) is the clinical expression for an obstruction of the blood flow in the vena cava superior, in its short course between the neck and the heart.
This syndrome is not uncommon in oncology, as the presence of enlarging metastatic lymph nodes is the main cause. From table 1.70 one can observe that the most frequently involved nodes are at the aortopulmonary (left) side, but also at the subcarinal and right paratracheal groups, contiguous to the vena cava superior.

The VCS is completely encircled by groups of lymph nodes that drain all the structures of the right thoracic cavity and of the lower part of the thoracal cavity. The progressive occlusion of the vein, through enlargement of the different lymph nodes, will led to an increasing back-pressure within the vein and the venous blood will 'pile up' so that the blood coming from the cranial parts of the body will seek alternative pathways (fig.1.13).

The main way is via the azygos system, left or right depending on the location of the obstruction, the internal mammary-epigastric system or the subcuta-neous veins, both at the wall of the trunk.

This has been classified by Stanford et al. into four types:
type 1. partial, about 90% occlusion of the VCS with an open azygos;
type 2. an almost complete obstruction of the VCS with open azygos and flow to the right atrium;
type 3. near complete or complete occlusion of the VCS with reversal of the azygos flow;
type 4. complete occlusion of the VCS and of the caval tributaries including the azygos system.

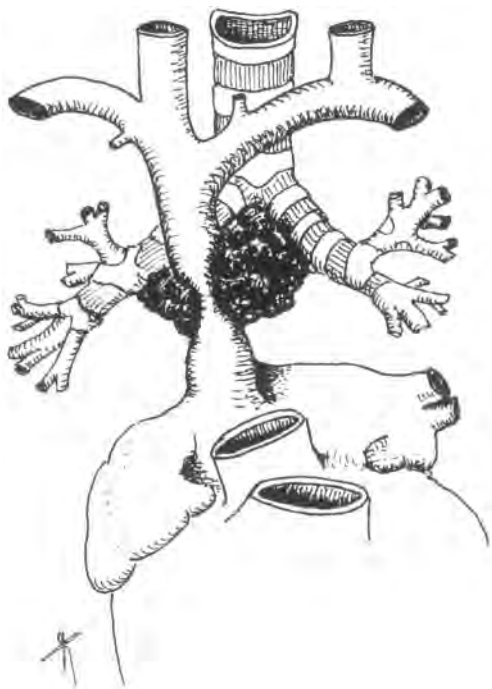

Fig.1.13 - Anatomy of the compression of the VCS

Though this is an attractive classification, it is difficult to apply, as venography is not always performed. The classification will also depend on the anatomical location of the tumor/lymph node mass.
One must remark that the VCS lies anterior to both pulmonary arteries, lateral to the heart and joins the right atrium at the right hilus, below the level of the carina (fig. 1.14).

Table 1.72 - Vena Cava Superior Syndrome
Primaries involved (N=67)
Data of Parish et al.

Bronchial carcinoma	45 (37%)
Squamous cell	12
Adenocarcinoma	11
Small cell carcinoma	12
Large cell carcinoma	8
Other histologies	2
Lymphoma	8 (12%)
Metastatic nodes	14 (20%)
Breast cancer	7
Testicular cancer	3
Thymoma	2
Unknown primaries	2

Etiology

Malignant tumors of the bronchus, as source of metastatic lymph nodes, are the main cause of VCSS. According to Armstrong et al., it probably occur in about 2 to 3% of cases, while it has been observed that is involved in 80%, a right-sided bronchial cancer. Chen et al. reported the occurrence in less than 2%, but in 7% of the small cell cancers at presentation. In the different series reported it amounted between 50 and 80% of the VCSS. A well documented series is the series of Parish et al. (table 1.72).
In the series of Armstrong et al., one case of metastatic cancer of the colon, one of the pancreas and one of a leiomyosarcoma of the uterus is mentioned. Remarkable is that breast cancer has a low frequency in all series, while it has proportionally a much higher incidence in esophageal compression. It should be remembered that the esophagus lies behind the trachea and that in breast cancer the compression occurs mostly at the middle third, through subcarinal lymph nodes.

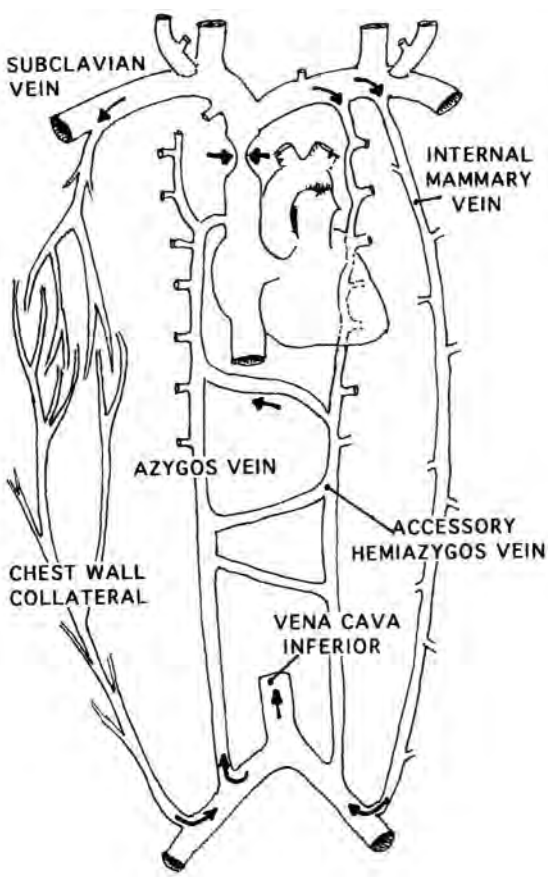

Fig.1.14 - Different possibilities of resultant collateral circulation caused by compression of the VCS

Symptoms

The onset is usually insidious. The patient will at first remark some collar discomfit and feel somewhat more oppressed in supine position. When the syndrome is full-blown, the characteristic features will be observed (table 1.73). Less frequent symptoms are vocal cord paralysis and Horner's syndrome. The most prominent are the pronounced dilated veins all over the abdominal and chest wall (fig. 1.15).

Table 1. 73 - Vena Cava Superior Syndrome
Symptoms and Signs
Literature Overview

Symptoms		Signs	
Dyspnea	65%	Neck venous dist.	66%
Facial swelling	50	Facial edema	45
Arm swelling	15	Chest wall veins	55
Dysphagia	10	Facial plethora	20
Chest pain	15	Cyanosis	20
Cough	25	Edema of arms	15

Radiology Findings

The most interesting data were provided by Armstrong et al., stressing the fact that right-sided bronchial cancers are in the majority (table 1.74).

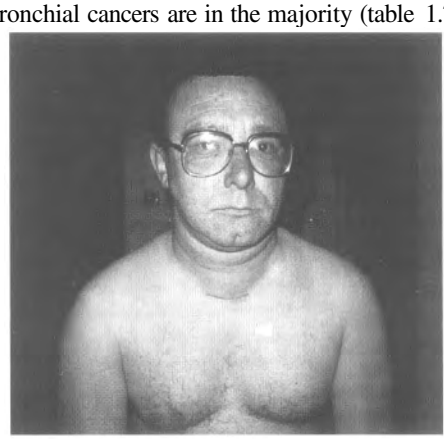

Fig.1.15 - Pronounced dilatation of the veins at the thoracacic and abdominal wall in a patient with the syndrome of Vena Cava Compression (from the files of the author)

Table 1.74 - Vena Cava Superior Syndrome
Radiologic Features in Bronchial Cancers (N=107)
Data of Armstrong et al.

Superior mediastinal mass (with or without effusion, pulmonary lesions)	26
Superior mediastinal and hilar mass	17
Sup.. mediast. mass and RUL-mass	6
Sup.. mediast., RUL and hilar mass	7
Sup. .mediast. mass, hilar N, bilat. effusion	1
Bilateral hilar adenopathy	1
Widened mediastinum	2
Right hilar mass with atelectasis	6
Right hilar mass without atelectasis	17
Right upper lobe mass	3
Right middle lobe mass	1
Right pleural effusion	2
Left upper lobe mass	4
(X-ray not available)	14

An upper mediastinal mass was observed in 60% of the patients, an hilar unilateral or bilateral in 41% and a right upper mass in 13%. This allows us to conclude that most occlusion of the VCS probably occurs in the paratracheal segment.

Diagnosis

Clinical symptoms readily provide the diagnosis. Etiology will be obtained by a transthoracic needle biopsy or a bronchoscopy, while CT will allow a good evaluation of the thoracic pathology, if the patient can sustain the supine position.

Cardiophrenic Nodes

A number of reports focus on a particular site of the mediastinum, the anterior diaphragmatic lymph nodes. Other authors have named them the paracardial or cardiophrenic lymph nodes (CPN).
It would seem that a careful retrospective examination of plain radiographs and now of the CT, can disclose some metastatic nodes, possibly not until they have developed into large masses. To to our knowledge, it was Libshitz et al. who first focussed attention on them (fig. 1.16).

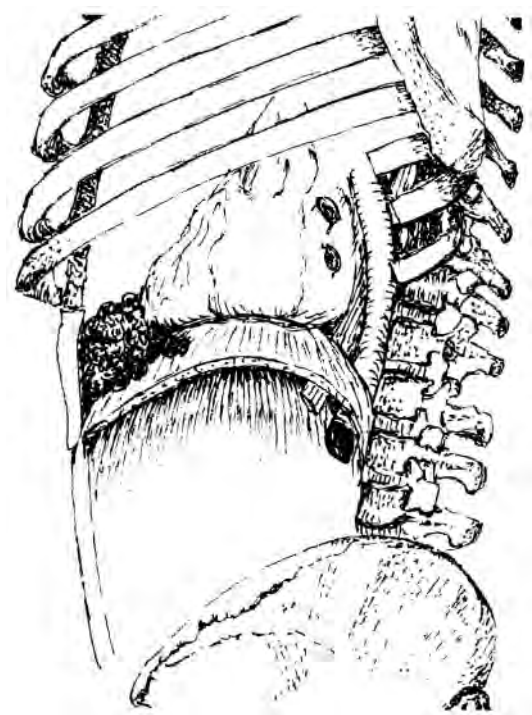

Fig.1.16 - A lateral view of the open thorax, showing the anterior diaphragmatic nodes.

The anterior diaphragmatic nodes, located at each side of the xyphoid and behind the anterior end of the seventh rib and on the anterior edge of the diaphragm, can be grouped with the pericardial nodes, and termed the cardiophrenic nodes. The afferent vessels are from the upper and lower surface of the diaphragm, the surfaces of the liver and from the anterior abdominal wall. They drain further to the internal mammary nodes.

Schwartz et al. distinguish three separate clusters:
1. the anterior, prepericardiac or anterior diaphragmatic nodes;
2. the middle or lateropericardiac, and
3. the posterior nodes

Libshitz et al. demonstrated invasion of these nodes (as seen on CT), mostly by lymphomas, but also in several cases of breast cancer, colon and bronchial cancer. Several other neoplasms had metastases there, but more details were not given. Vock remarked that supra and infradiaphragmatic tumors could also metastasize in these nodes. The incidence of enlarged CPN nodes occurred in 2.6 per oncology patients in the 151 consecutive chest CT (Aronberg et al.) Recently a number of reports have appeared which draw the attention to this metastatic location in ovarian carcinoma (Holloway et al.). Calcified nodes at that site were described by Ferrotti et al., in a patient with ovarian carcinoma.
The site is probably involved in advanced intra-abdominal malignancies.

The sternal metastasis from an ovarian cancer in a patient reported by Noguchi et al., is most probably the ingrowth of such a metastatic node in the sternum and not a genuine sternal metastasis.

Imaging - Diagnosis

As chest radiography is largely aspecific, CT of the mediastinum will adequately delineate the mediastinal involvement. Fine needle biopsy or bronchoscopy with transtracheal biopsy may be needed to refine or confirm the diagnosis.
CT will more accurately define the characteristics of mediastinal masses. Mediastinal adenopathies are clearly visible and their dimensions and nature readily evaluated.

Differential Diagnosis

Chest radiography cannot distinguish metastatic lymphadenopathies from lymphoma, sarcoidosis, tuberculosis, histoplasmosis and even primary bronchial carcinoma.

METASTASES to the FEMALE BREAST

Metastases to the breast are not uncommon in oncology practice. They occur in the female and in the male breast as well, but the primaries involved differ clearly.

While primary tumors of the breat are common, metastases of other tumors to the breast is relatively rare.
As they are clinically undistinguishable from a primary, diagnosis can be difficult even when the patient is known to have been treated for another tumor. The prompt recognition of such a tumor from a cytologic or bioptic fragment by the pathologist is important in order not to miss the other primary, as this may have prognostic implication.

Incidence

Since many cases remain probably occult, the incidence of metastases to the breast is unknown. It has been stated that if 100 women are treated for a 'breast tumor', one is likely to be a metastatic tumor. From some autopsy studies, the frequency ranges from 1.7 to 6.6%. The variation is probably due to the inclusion of heterolateral breast metastases or of hematologic malignancies.
Melanoma and bronchial cancer probably accounts for 50% of all the breast secondaries.

Pathways

A metastasis to the breast may occur along the lymphatics or is blood-borne.
Lymphatic metastasis occurs when a breast cancer spreads across the anterior chest wall, via the transthoracic pathway. They are not true metastases within the breast parenchyma. Metastases from the heterolateral breast are difficult to differentiate from a new primary within the heterolateral breast, unless it involves skin or subcutaneous tissue.

In fact, all secondaries from an extramammary tumor are hematogenous. Lymphatic spread could be invoked via the subclavian or retrosternal (anterior mediastinal nodes) in the event of invasion of the abdominal wall. Paulus et al. consider a third type such as found in the hematologic malignancies.

Table 1. 75 - Blood-Borne Metastases to the Breast
Primary tumors involved
Data of Paulus et al., 1982

	Literat.	Autopsy	Author	All
Melanoma	38	8	10	56
Bronchus	37	8	10	43
Ovary	16	--	5	21
Sarcoma	15	3	4	22
Gastrointestinal	10	1	--	11
Genitourinary	13	2	--	15
Other	28	5	1	34
Total				202
Hematologic	57	8	19	84

Involved Primaries

Reviews of the literature indicate that melanoma is the most frequent source of a breast secondary, followed by soft-tissue sarcoma and ovarian carcinomas (table 1.75). In 1989, there were less than 300 reported cases in the literature (Alexander et al.).
The author reviewed 20 reports involving more than one case with breast secondaries (table 1.76).

Type 1 - presentation

Metastatic disease of the breast was the first manifestation of malignant disease in 25 to 40% of all reported patients. Small cell bronchus carcinoma is the most frequent 'unknown' cancer. Of 51 patients reviewed (7 males), 16 patients were type 1 presentations (Hajdu).
A number of renal cell cancers have been detected at breast cancer screening.

Table 1.76 - Metastases to the Female Breast
Literature review , 20 series (') totalling 176 cases

Gynecology:	Cervix Uteri	3 cases
	Endometrium	3
	Choriocarcinoma	1
	Fallopian Tube	1
Gastrointestin.	Esophagus	1
	Stomach	6
	Pancreas	3
	Colon	3
	Rectum	4
	Liver hepatoma	1
	Liver Cholangio	1
Bronchial	Small Cell	22 (12.5%)
	Non-small cell	23 (13.0%)
Head and Neck		8
GenitoUrinary	Kidney	6
	Urinary Bladder	1
Skin	Melanoma	33 (18.7%)
Thymoma		1
Thyroid		4
Cerebrum (astrocyt-ependymoma)		2
Lymphoma-Leukemia-Myeloma		33 (18.7%)
Mesothelioma 2		
Sarcoma		3
Neuroblastoma		1
Carcinoid		5
Unknown		5

Data from Sandison 1959 (N=7); Deeley 1965 (N=8) Silverman 1974 (N=11); Verhaeghe 1976 (N=7); MacIntosh 1976 (N=29); Vermeer 1977 (N=4); Vizel 1981 (N=1); Nielsen 1981 (N=15); MacCrea 1983 (N=15); Silverman 1987 (N=15); Sneige 1989 (N=17); Alexander 1989 (N=2); Amichetti 1990 (N=14); Vergier 1991 (N=8) DiBonito 1991 (N=12); Umbricht 1992 (N=2); Chaignaud 1994 (N=9); Iwaszkiewicz K. 1995 (N=2); Domansky 1999 (8 cases)

Interval

In patients with a known tumor, the time between diagnosis of the primary and of the metastases averages 2 years. In some reports more than 75% occurred within one year (review by Alexander et al.).

Pathology

Two-thirds of the secondaries appear in the upper

outer quadrants, as is common in the primary breast cancer. Bilaterality will probably be found in 25%, and axillary lymph nodes in 15%.
Pathological features at biopsy are the absence of 'in situ' or intraductal carcinoma. Malignant cells are mainly peritubular and intraparenchymal. The histology will probably be similar to that for the primary and is indicative in type 1 -metastases.
Metastatic sarcomas occur most frequently in children or young adults.

As far as side is concerned, earlier reports find slightly more on the left: Hajdu et al. have 53% on the left and 8% bilateral.

Imaging

Despite the clinical similarity of breast secondaries, radiology (mammography) can help distinguish them from a primary breast cancer.
Cross-lymphatic metastases are in fact skin or subcutaneous spread from the heterolateral primary and must be discerned on clinical ground. They are not true metastases within the breast parenchyma. We will not discuss them further.

A mammogram of a blood-borne metastasis shows discrete or semidiscrete nodules, either single or multiple and of varying sizes. Cutaneous permeation can occur in melanoma, as well as uni- or bilateral axillary lymph nodes. Microcalcifications have been observed, but they were virtually all psammoma bodies from an ovarian carcinoma (Paulus et al.).
A discrete nodule is difficult to differentiate from a cyst or fibroadenoma, but knowledge of a previous tumor must make such a finding very suspect.
One should remember that 10 to 20% of the metastases are not visible on a mammogram.

Diagnosis

The most important problem is the differential diagnosis with a primary breast cancer.
The diagnosis can be inferred on clinical grounds, but a FNAC should confirm the diagnosis or even indicate the primary when that is unknown. The temporal relationship is an important factor in the definite diagnosis.
Cytology has been proven to be an excellent method for detecting metastases. The characteristic cytologic appearance of the cells facilitates the diagnosis as it is similar to that of the primary. There are, however, usually problems with epidermoid cancers.
The presence of signet-ring cells can lead to difficulties as an aggressive variant of lobular carcinoma contains signet-ring cells which need to be distinguisheded from a metastatic stomach cancer (Briest et al.).

Bibliometry

If the literature references are classified according to primary and site of metastases, the number of reports will give some indication of the relative frequency. The most frequent primaries involved in case reports are ovarian cancers and carcinoids. Rare cases can, however, prompt more frequent reports than more common ones. Some reports also contain more than one case. Table 1.77 must be compared with table 1.76.

Table 1.77 - Metastases to the Female Breast
Bibliometry of number of primary in the case reports
Review by the author 1998

Carcinoid	21	Meningioma	1
Ovary	21	Kidney	11
Cervix Uteri	14	Rectum - Colon	3
Choriocarcinoma	3	Sarcoma	11
Endometrium	1	Thyroid	8
'Gynecologic'	1	Tuba	1
Bronchus	6	Urinary Bladder	2
Stomach	8	Head & Neck	4
Melanoma	11	Pancreas	1
Germin.Ovary	1	Myometrium	2
Thymoma	2		

METASTASES to the MALE BREAST

Metastases to the breast in males are much rarer than in female patients. They have been reported mainly from prostatic and bronchial cancer. Estrogen therapy has been cited as a causative factor.
A review in 1969 by Sandison disclosed 8 cases from an autopsy study of 139, or 7.2% (table 1.78). The majority were lymphomatous cancers.
Since then, reports on metastases from the thyroid, prostate and the urinary tract have appeared.

It is difficult to distinguish the metastasis from gynecomastia although this can be a marker for a malignancy elsewhere. An important point is the absence of malignant cells within the ductal system as a sign of metastasis.
Fine needle cytology or/and biopsy seems appropriate, as imaging has probably not much to offer.

Table 1.78 - Metastases to the Male Breast
Primary Involved
Literature Review by Sandison 1969

Bronchial cancers	1
Melanoma	1
Lymphoma-Leukemia	8

Bibliometry

We found 25 literature reports on prostate cancer metastatisizing to the male breast and only 3 from a testicular cancer, 2 from the bronchus, one from an urinary bladder cancer and one from a thyroid carcinoma. Only 3 reports make a survey.

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Caution: References are given for documentary purposes. Not all have been reviewed or used in the redaction of the text. We do not claim completeness of data. The references are as much as possible grouped per subject heading. For some headings, only reports after 1974 are listed.

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2

METASTASES to the ABDOMINAL ORGANS

In this chapter we discuss the metastases in the abdominal organs, excluding the digestive tract and genito-urinary system.

METASTASES to the LIVER

Many malignant tumors, if not all, metastasize to the liver, an organ at the crossroads of the portal and abdominal venous system and receiving arterial blood almost directly from the heart. The liver is a common site for metastases.

Pathways

Metastatic cells can reach the liver by several routes. The double vascularization of the liver through the arteria hepatica and the vena portaeprovides two opportunities. A lymphatic route along the portal tract is not uncommon, especially in gallbladder cancers but has also been described for other primaries, mainly the ovaries (fig.2.1).

Table 2.1 - Metastases to the Liver
Pathways of cells to the liver

Arteria Hepatica, from lung parenchyme
Vena Portae for intraabdominal organs
Invasion of portal vein from retroperitoneal masses
(genito-urinary tumors)
Lymphatic pathways
pancreas, stomach, gallbladder
Lymphatic invasion of thoracic duct,
followed by systemic spread:
thoracal tumors such as breast and lung
Local direct invasion
cancer of organs adjacent to liver:
gallbladder, colon, adrenal
from peritoneal implants of ovarian cancer

In addition to this vascular spread, contiguous invasion from neighbouring cancers as from the gallbladder and even colonic cancers occurs, but cannot be considered as true metastases (table 2.1).
Spread of tumor cells from abdominal organs draining to the portal system, will obviously occur through this avenue. Invasion in the portal vein has been described from retroperitoneal masses, particularly at the pancreatico-biliary axis.

Direct access to the liver along a lymphatic pathway from cancers of the pancreas, the stomach and the galbladder has been described.
It is evident that the liver parenchyme can be reached from the lungs through the arterial blood supply, after having been reached either through the caval circulation or through the ductus lymphaticus and the superior caval system.
A direct invasion towards the liver is common for the gallbladder tumors, but has also been observed for colonic and adrenal tumors.
Growth into or within the liver capsule is regularly observed from peritoneal implants on its surface from ovarian cancers. This is discussed more extensively in the chapter on ovarian cancer.

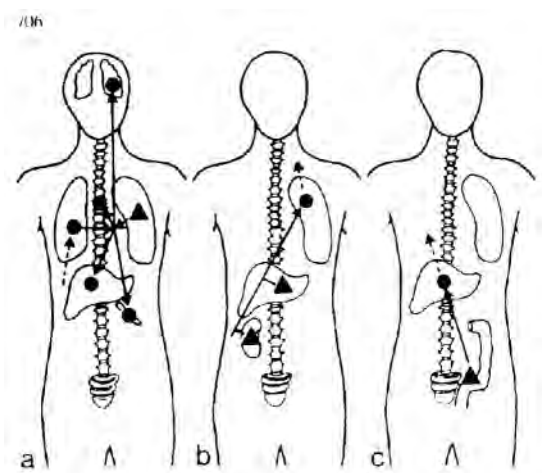

Fig. 2.1 - Schematic outline of the different pathways for liver metastases - a. tumors reaching the liver through the art.hepatica also reach other organs almost simultaneously (bronchus, mamma); - b Tumor cells spreading through the vena cava can metastasize later through the arterial system; - c. All sites draining (mainly) through the portal system reach the liver first.

Hemodynamics

The liver normally receives 75% of its blood supply via the portal vein and the remaining 25% via the hepatic artery. This pattern is altered in metastases.
The growth of the metastases involves a change not only in size but also in their blood supply.

The dominant arterial supply is accompanied by a less preserved portal supply. The latter cannot be underestimated, because the highest proliferative activity is at the periphery of the tumor. This must be kept in mind as an arterial embolization will not always reach the periphery and will fail in a number of cases.

Angiographic studies in vivo have shown a wide variation of blood supply to the hepatic metastases. Hyper-vascularity with hypertrophy of the hepatic arterial supply is one extreme while the absence of contrast uptake isanother.

Study of macrometastases has revealed that all have the same vascular pattern, although metastases of the same primaries have a different angio-architecture (Strohmeyer et al.).

The arterial blood supply is organized into two different types, a central one and a peripheral type.

The central type consists of one main artery with a hilus-like approach and branching within the tumor. The artery is not accompanied by a portal vein.

The peripheral type consists of a circumferential arc, from which smaller arteries infiltrate the nodule (fig.2.2).

Intermediate types are observed.

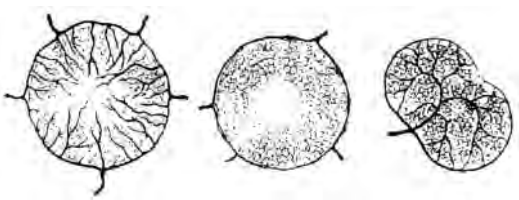

Fig..2.2 - Schematic drawing of the arterial supply of liver metastases: at left a hypervascular peripheral type, middle hypovascular and at right the central type (Strohmeyer et al., after Rubin et al.)

The portal blood supply is visible only in a part of the nodules, mainly along a central-type artery. In about half, the periphery receives portal supply from adjacent sinusoids. In one third, a portal vein reaches the center. An important aspect is that one third shows throm-bosis at the center, but in others also at the periphery.

A fact usually neglected in studies is that the venous supply seems to be altered to an even a greater extent than the portal supply. In only one tenth, the vessels are visible from the center of the nodule, with signs of compression and destruction all over.

Additional micrometastases, smaller than 200μm, can be observed within 1cm of the macrometastases in the sinusoids.

Small metastases are supplied by the surrounding hepatic sinusoids. As they grow, newly formed blood vessels will supply them. Other authors have shown an internal vasculature, derived from the hepatic artery, in tumors smaller than 0.5mm. The blood supply switches from sinusoidal in the replacement and sinusoidal pattern to vascular when the pattern evolves to a more expansive type. This could explain why arterial embolization or infusion has a variable effect, due to the correlated vascular pattern. As tumors enlarge, the peripheral portal vessels will be compressed, in spite of arterio-portal communications at the periphery. This explains the partial preponderance of portal circulation when arterial occlusion ensues.

Furthermore, the metastases rely quite a long time on the arteria hepatica, at least at their center. At the periphery, however, blood supply seems to be mixed with blood from the portal vein. The problem of the portal vein is the incidence of tumoral thrombosis or obliteration through tumor cells. The existence of satellite nodules or metastases around larger ones can only be explained through the venous intrahepatic drainage from the first (Eder et al.).

Several studies have shown arterio-venous shunts at three levels in the liver (Lin et al.):

1. peribiliary arterial plexus anastomoses with the portal vein;
2. the vasa vasorum of the portal vein are in direct communication with the portal vein, and
3. direct arterioportal connections in the sinusoids.

These collaterals will mitigate the therapeutic success of hepatic artery embolization, although success has been claimed to a limited extent. Moreover the collaterals will soon compensate for the occlusive effect and the arterio-portal connections will take over (Lin et al.). Other experiments have shown that more than twice as much nutrient substrate is delivered by the hepatic artery per volume of tumor relative to the liver as by the portal vein (Ridge et al.).

Anatomic Distribution

The distribution of the metastases within the liver has been studied by Schulz et al. on autopsy livers. Forty percent of them reached the surface while the other 60% were invisible at the surface because of their deposition in the central parenchyme. It is striking that in 8% of the examined livers, there were only superficial metastases and in 12%, only deep metastases. The correlating primaries were not reported. In a similar study, Strohmeyer et al. found that of the 71 livers studied, metastases were present in only 11 at the right and in 2 at the left half. There were proportionally more metastases in the right than in the left half, in a ratio of 3.4 to 1. This correlates however with the normal volume ratios. No difference was found between the metastases which arose via the portal veinand those via the hepatic artery. When the number of metastases was compared to the liver volume, no particular propensity was observed, meaning that the distribution was homogenous and did not 'favor' a particular segment (table 2.2).

Table 2. 2 - Metastases to the Liver
Density of liver metastases
Data of Strohmeyer et al.

N / liver volume	Spread	Left	Right	Total
	Portal	1.030	0.775	0.836
	Arterial	1.167	1.003	1.036
	Total	1.121	0.926	0.968
Vol of Metastases/liver volume				
	Portal	22.2%	24.5%	24.0%
	Artery	15.0	18.1	16.9
	Total	17.4	20.3	19.3

Differences are not significant p>0.05)

Overall, at autopsy, about 20 to 25% of the liver volume has been replaced by a metastatic mass.

According to the number of metastases in the liver, the same authors could distinguish three groups:

1. livers with only solitary metastases, either large or small. Of their 34 patients, 9 had single metastases or 26.4%, of which seven were smaller than 1cm.
2. livers with one or only a 'few' small metastases. This was observed in 10 of the 34 livers or 29.3%, all smaller than 1cm. Almost all concerned adenocarcinomas.
3. livers with only a 'few' small and large metastases: most of the studied livers (22/34 or 64.7%) had small and large metastases close to each other. In 19 patients there were up to 9 large metastases and in 3 more, between 17 and 34 nodules.

In their study of 34 metastatic livers, there were 671 metastatic nodules with a mean diameter of 1cm.. Twenty percent had large ones, with a mean diameter of 1.6 cm and the other 80% had a mean of 0.6 cm. One remarkable aspect is the constant overall proportion of large to smaller ones, with a value of 1 to 3.2 to 3.9 (table). This seems to correlate with the type of primary (table 2.3).

Table 2. 3 - Metastases to the Liver
Pathology Data - Ratio Large to Small
Data of Schulz et al. 1992

Total large	N Patient	Large/small
1 - 3	10	14-45 or 1:3.2
4 - 9	19	72-285 or 1:3.9
10-24	3	60:239 or 1:3.9

Primary	N pat	Nmeta	Large/small
Colon	8	56	1:1.6 (')
Bronchus	8	74	1:3.1
All cancers(°)	26	615	1:4.5

(°) without solitary the value is 1:1.2
(°) without colon cancer patients

These data show that when one metastasis is detected, there is a large probability of finding 3 to 4 more smaller metastases in the neighbourhood. This value seems to be smaller for colonic tumors, so that the results of resection of metastases could statistically be much better in these cancers than in the other ones.
The homogenous distribution of the metastases was challenged by Hata et al. They studied the livers of 217 metastatic gastrointestinal tumors and concluded that there are more metastases in the posterior segment in patients with left colonic cancer and more in the medial segment in rectal cancer. For all the colonic cancers, there were significantly more metastases in the right half of the liver (table 2.4).

Table 2.4 - Metastases to the Liver
Intestinal tract tumors, data of Hata et al.1995

	N	Right	Left	
Esophagus	7	2	5	°
Stomach	30	12	18	°
Right Colon	12	8	4	p<0.05
Left Colon	17	13	4	p<0.05
Rectum	16	7	9	°
Bile duct	7	6	1	°
Pancreas	5	3	2	°

(°) not significant

An explanation for the possible and apparently hypothetical left-right difference, is the 'streamline' phenomenon (fig.2.3). This was demonstrated by some authors. Splenic blood drains predominantly into the left lobe, whereas mesenteric blood should drain preferentially into the right half of the liver. Tumor cells administered to rats via the portal vein showed a different distribution in the liver depending on the site of injection (Hata et al.). Other authors have barely seen a difference.

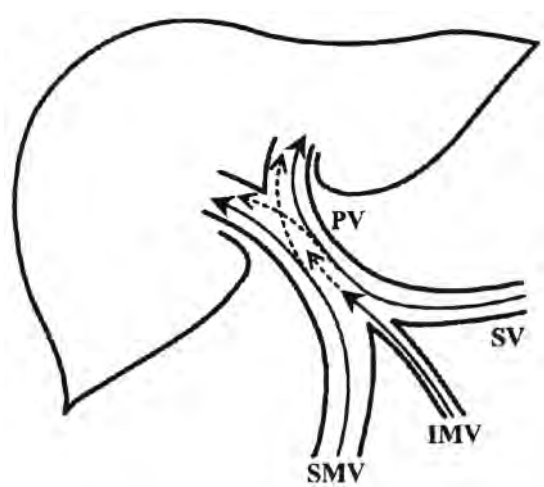

Fig.2.3 - Schematic representation of the hypothetical streamline flow to the liver. From the superior mesenteric vein (SMV) the blood should preferentially flow to the right half, and from the splenic vein (SV) to the left half. Blood from the inferior mesenteric vein (IMV) drains to both lobes (from Shirai et al., with permission).

If, at first glance, there are more metastases to the right lobe, it is probably because its volume is larger and is

more likely to contain more metastases. About one third of the patients with colorectal liver have metastases in one lobe only. Bilateral deposits are more common in breast cancer and melanoma.
In a retrospective study on 270 patients with documented liver metastases from a colorectal carcinoma, there was an overall preponderance of right lobe metastasis independent of the site of the primary (Holbrook et al.) (fig.2.4). The number of metastases in the left lobe was higher for the lateral colon, but only when there were overall four or less metastases present (table 2.5, fig.2.5).

Table 2. 5 - Metastases to the Liver
Left-Right Repartition in Colorectal cancer
Data of Holbrook et al. 1996

All metastases
Right lobe (V-VI-VII-VIII) 736 M (63%)
Left lobe (II-III-IV) 430 M (37%) p<0.001
II-III 69% and IV 31%
Four or less metastases
Right lobe 258 (75%)
Left lobe 88 (25%) with (p<0.001)
68 in II-III and 20 in IV
M: number of metastases

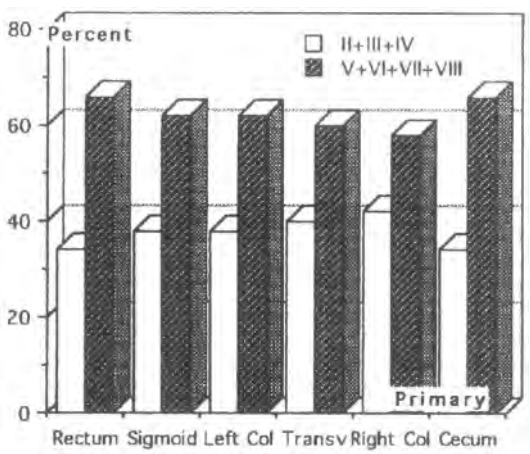

Fig.2.4 - Proportion of metastases within the right compared to the left, half depending on primary location in the colon (drawn from data of Holbrook et al.).

No statistically significant difference was observed according to the primary site within the colon, neither was a difference in metastatic location within the liver. We think that all the different and contradictory results are due to different interpretation. When the right lobe is a larger 'basket', it is very probable that more metastases will settle in it, so that a statistically 'significant' difference between both lobes is a statistical misnomer and misjudgment.

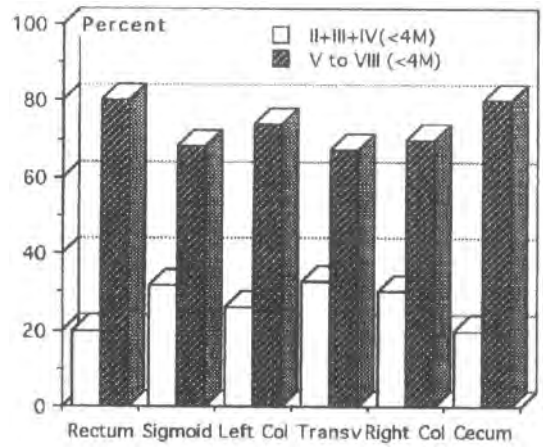

Fig.2.5 - Proportion of metastases within the right compared to the left half depending on primary location in the colon and when less than 4 metastases are present (data of Holbrook et al.).

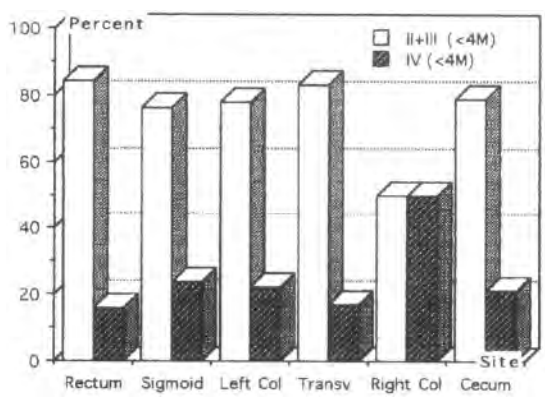

Fig.2.6 - Metastases in the liver - Repartition within the left lobe, when fewer metastases are present in patients with rectocolon tumors. (Drawn from data of Holbrook et al.)

The streamline effect is probably demonstrable in standard situations, but movement, gravity and hemodynamics over a 'day-life' will normalize the anatomic distribution. This was also the conclusion of Wigmore et al., who recently published data on the problem after a prospective study on 207 patients with colorectal cancer. No anatomical difference was observed in the distribution within the liver segment according to the site of the primary within the colon (fig.2.7).

Solitary metastases

Solitary metastases are in principle amenable to surgical resection. There is therefore some value to knowing how frequently this situation occurs.
The frequency of solitary metastases varies according to the authors and the method of study of 6% (Pickren et al.) and 8% (Eder et al.) of the patients with liver

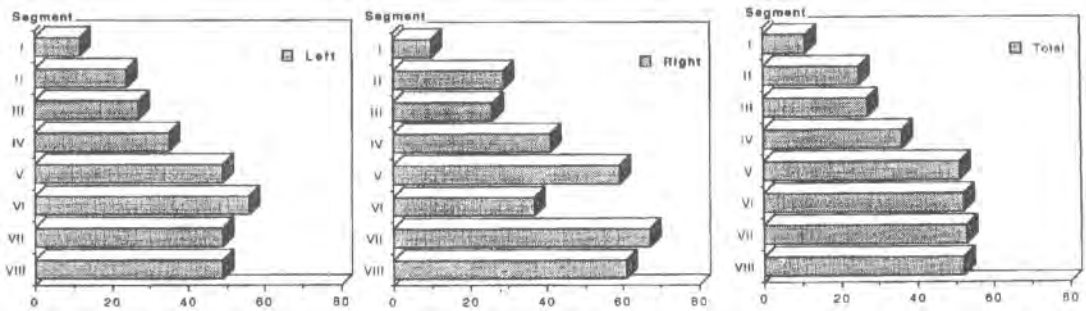

Fig.2.7 - Distribution of metastases within the different liver segments. No proportional difference is found according to the site of the colonic primary (rectal cancer is included in left sided) (drawn from data of Wigmore et al.)

metastases at autopsy. This must, however, also depend on the primary involved, since for colonic cancers, more than 30% of those with liver metastases had solitary metastases.

The relative contribution of both large vessels can be estimated if the statistical data are examined for each type of primary. The histology type of the primary has also an influence, as small cell bronchial carcinoma for example, has a much larger incidence of liver metastases compared with the other types. (This is discussed in Chapter 7).
In any case, the incidence of liver metastases is much higher from the organs draining to the liver via the portal vein. This also explains why in this group there are more solitary liver metastasis without other parenchymal than for those metastasizing predominantly via the arteria hepatica, such as bronchial, mammary or prostatic cancers. This observationhas led to the so-called cascade theory. Liver metastases from the portal system will generate other metastases in a following second step along the vena cava and subsequently through the arterial system.

It has been estimated (Weiss) that tumors draining through the portal vein to the liver have a tenfold higher incidence of hepatic metastases than the others. It is strange, however, that there is such a high incidence of liver metastases in testicular cancers, as this tumors drains through the vena cava. Other tumors such as mammary and bronchial carcinomas do not have a significantly lower rate than tumors of the upper abdomen.

Incidence

There is a large volume of data at hand concerning liver metastases for the various primaries and for different stages of the neoplastic process, either at diagnosis, during the follow-up or at autopsy.
Liver metastases are found in autopsy studies in 40-50% of all cancer patients. The most frequent primaries in order of frequency, are the bronchial, the mammary, rectocolic and uterine cancers. When each primary is considered, half of the patients dying of stomach or mammary cancers have hepatic metastases (table 2.6). Another remarkable fact, and one which confirms the seed and soil theory, is the correlation between the histology type and the incidence of hepatic metastases. Melanomas and adenocarcinomas have a much higher propensity (table2.7).

Table 2.6 - Metastases to the Liver
Autopsy Incidence Rate
Literature survey Bedossa et al.

Pancreas	50-70%	Bronchus	35-50%
Rectum - Colon	20-35	Breast	45-60
Stomach	35-50	Kidney	27-50
Urin.Bladder	35-50	Thyroid	<40
Testis	50-80	Uterus	<40
Ovary	10-15	Prostate	<40
Melanoma	70%	Oropharynx	<40
Neuroblastoma	40-80		

Table 2. 7 - Metastases to the Liver
Influence of histology of the primary on rate
Data from Weiss

Melanoma	60%
Neuroblastoma	60%
Adenocarcinoma	48%
Sarcoma	34%
Epidermoid cancer	18%

There is an age-dependance for the incidence of liver metastases, as has been noted in the autopsy studies of Basserman et al. (fig.2.8,next page). In women the incidence of liver metastases from mammary carcinomas gradually decreases with age, while it increases for liver metastases of stomach and colon cancer. The same trend is observed in men for these cancers, while it decreases for pancreatic cancers.

Pathology

The macroscopic appearance of liver metastases can be classified in a similar way as hepatocellular carcinoma: nodular, massive and diffuse. The nodular type can be subdivided into solitary, multinodular and fused. There seems to be a certain correlation between the primary tumor and the macroscopic metastasis type (fig.2.10). In bronchial cancer only nodular metastases

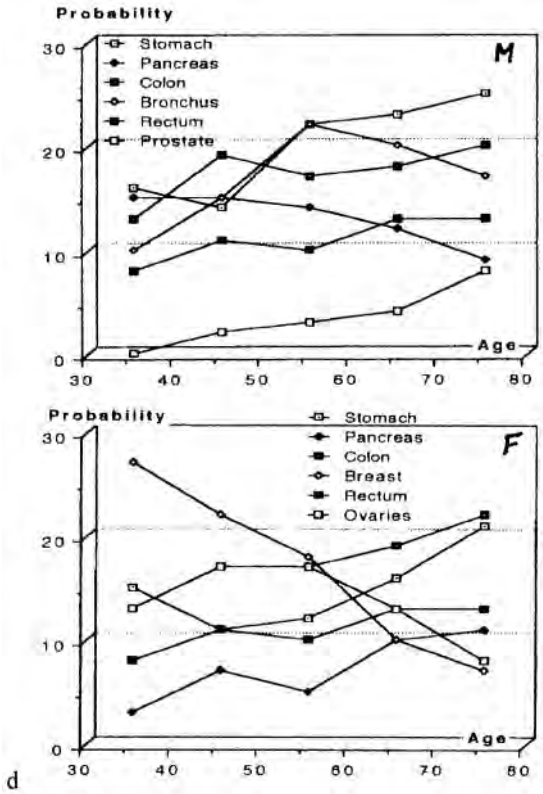

Fig.2.8 - Incidence of liver metastases in male (upper) and female patients (lower) coming to autopsy for different primaries according to age. (Redrawn from Basserman et al., with permission).

are present, while about one quarter of the stomach and bile tract cancer have massive metastases (Terayama et al.). They describe a portal tract-type metastasis when the portal tract is enlarged and linear or small nodular tumors are present in the vicinity, and consider it as lymphangiosis carcinomatosa.
With the exception of melanoma metastases, liver metastases are more lightly coloured. At palpation they are firmer than the surrounding hepatic tissue. Concentric growth with extension in all directions enlarges the nodules. Metastases at the surface sometimes umbilicate what can be explained by the presence of some infarction.

The growth site can be classified into three types:
1. a portal growth type with tumors growing within and/or along the portal tracts;
2. a parenchymal growth type, growing in and/or towards the hepatic parenchyma with little or no portal tract growth;
3. an intermediate type including both previous types (Terayama et al.).

Animal studies have revealed that metastatic cells first come in and implant in the portal endothelium in a limited portion of the sinusoids. Tumor cells can then migrate to a portal terminal and spread either to a nearby region or along a periportal lymphatic. This is referred to as a 'tertiary' metastasis. Willis has shown schematically the evolution of metastasis within the liver after cells have settled in digramatic form (fig.2.9).

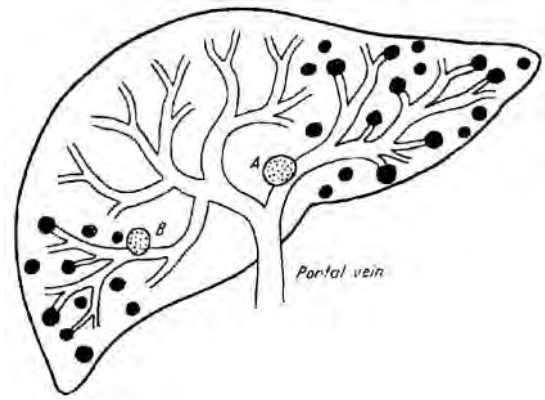

Fig. 2.9 - The evolution of liver metastases - At (A), an initial metastatic growth, invaded a main branch of the portal vein and produced daughter metastases throughout the corresponding lobe. At (B), an initial metastasis has invaded a peripheral branch vein and produced daughter metastases in a corresponding restricted region of the liver. (Willis R.A., The spread of tumours in the human body, Butterworths, ed.1973, with permission)

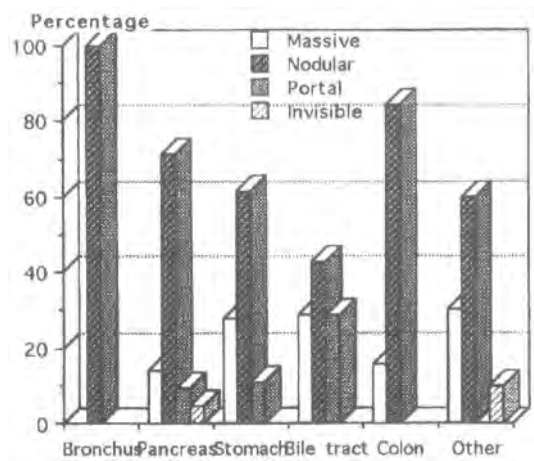

Fig. 2.10 - Metastases in the liver - Macroscopic type according to primary lesion (drawn from data of Terayama et al.)

The microscopic appearance or histologic growth pattern as seen at the boundary between tumor and hepatic parenchyma has been classified as follows:
1. Sinusoidal pattern
2. Replacement pattern
3. Encapsulated pattern
4. Expansive growth pattern
5. 'Unclassified'

In the sinusoidal growth pattern the tumor cells infiltrate into the sinusoid at the boundary of the metastasis, and the liver cells are left inside the boundary of the tumor.

In the replacement growth pattern the tumor cells grow within the liver cell plates. The replacing tumor cells are still in continuity with the liver cells.
Compression and destruction of the liver cells is a little more prominent than in the same pattern of growth of hepatocellular carcinoma.

In the expansive growth pattern, the tumor cells will compress the liver cell plates and sinusoids, resulting in atrophy of the liver cells. The border of the tumor is somewhat even and smooth.
An enclosing fibrous capsule around the individual metastatic foci is the mainstay of the encapsulated pattern.
Initially, metastases grow elliptically, reflecting the local vasculature pattern. When tumors expand, they become more spherical because of the slowed growth rate. The histologic pattern can best be observed in the small metastases, but the aspect and predominance of each pattern evolves with the size of the metastases. When small, the majority of metastases from bronchial and pancreatic cancers are of the replacement type, while at larger sizes (20 mm or more), the expansive pattern becomes the main type. On the other hand the sinusoidal pattern is predominant in the small metastases from stomachal, biliary tract and colonic cancers.
The different histology patterns apparently represent somewhat different phases in the development of the metastatic nodule and process.Any fibrous capsule and/or fibrous septa occur in 10 to 15% of the colonic cancer and in those of the bile tract (table 2.8).

Table 2. 8 - Metastases to the Liver
Histology Pattern in small nodules (<1mm)
Data of Terayama et al. 1996

Primary	Pattern Replac.	Expans.	Sinusoid.
Bronchus	69.7%	10.6%	13.6%
Pancreas	79.3	0	17.2
Stomach	39.4	6.1	48.5
Bile tract	26.7	6.7	66.7
Colon	66.6	6.7	26.7

Table 2.9 - Metastases to the Liver
Histology Pattern in small nodules (>20mm)
Data of Terayama et al. 1996

Primary	Pattern Replac.	Expans.	Sinusoid.
Bronchus	31.3%	62.5%	0%
Pancreas	25.0	50.0	4.2
Stomach	0	84.6	7.7
Bile tract	15.8	47.4	0
Colon	7.7	76.7	0

The same authors could not observe any significant difference in the mean weight of the metastatic liver according to the primary cancer (fig.2.11).

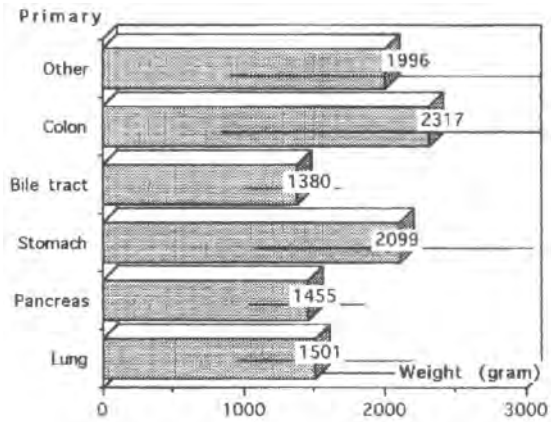

Fig.2.11 - Metastases in the Liver - Mean weight of the liver according to primary tumor - Drawn from autopsy data of Terayama et al. (Lung N=24; pancreas, N=21; stomach N=18; Bile tract N=14; Colon N=13; Other N=10)

Cases of metastatic carcinoma resembling lymphangiosis carcinomatosa of the lung are classified in the same way as the portal tract type. Here the tumor cells enter the interstitium along the lymphatics, spread from the hepatic hilum to the peripheral liver along the portal tracts, and linear or small nodules are observed in the vicinity of the portal tracts. This type occurs frequently in poorly differentiated adenocarcinoma, particularly in gastric, pancreatic and bile tract cancers.
The size of the metastases is variable and seems to be correlated with the number. The more nodules are present, the more they are uniformly small. Solitary metastases can reach huge dimensions, replacing up to half the liver and dramatically enlarging its volume.
Yamanami et al. have developed a stereologic method of estimating the number and the size distribution of metastases in the liver. The number of metastases is much higher than could be expected. More data are much needed. Estimates of the number, as tested in 31 autopsy cases, have ranged from 10 to 3.2×10^5. From their data, we can deduce that the mean number of metastases and the mean size of the metastases is much higher when from the stomach than when from rectocolon or pancreas (table 2.10).

Table 2. 10 - Metastases to the Liver
Size and Number of Metastases
Data of Yamanami et al. 1999

	N cases	Mean Size	Mean Number
Stomach	8	9.74 mm	39.800
Pancreas	15	1.70 mm	10.590
Recto Colon	5	3.86 mm	29.500

Hepar Lobatum

Hepar lobatum is an acquired liver deformation with irregular lobulated contours and so-called crevices and linear depressions. First described in tertiary syphilis,

a number of cases have been reported resulting from diffuse carcinomatous involvement. It was named 'Kartoffel-leber' by Kalk in 1954. By 1996 Gravel et al, were able to enumerate nine cases, almost all from mammary cancers of ductal origin and one from a stomachal adenocarcinoma. While the diagnosis was previously mainly made at autopsy, it can now be recognized by CT examination.

The pathogenesis is probably due firstly to an episode of intrahepatic tumor necrosis involving a large area with subsequential lesional tissue collapse, followed by a phase of tissue healing with contraction (Gravel et al.). Two factors are thus probably responsible: scirrhous stromal reaction to carcinoma and/or vascular impairment due to infiltration (Honma).

Influence of the Status of the Liver

A particular demonstration of the 'seed and soil' theory on the settling of metastases is the influence of a number of states of the liver on the incidence of metastases.

The first fact is the lower rate of liver metastatic disease in cirrhotic patients. This has been observed by several authors. The type of cirrhosis does not influence the metastatic rate. It seems that a cirrhotic liver is not an adequate soil for the proliferation of metastatic cells. This was well illustrated in an international study by Melato et al. The same rate was observed both in Italian as in Japanese patients as well (table 2.11).

Table 2.11 - Metastases to the Liver
Influence of cirrhotic liver on its incidence
Data by Melato et al. 1989

	Presence of Liver metastases	
Patients	Cirrhotic	Non-cirrhotic
Italy	26/138 19%	88/216 41%
Japan	3/22 13%	205/395 51.6%

This is opposite to what is observed in primary heptocellular carcinoma, where there is a much higher incidence in cirrhotic livers.

The literature on this subject was recently reviewed. The overall crude metastatic rate to a normal liver was 37.3% while it was 'only' 23.7% in cirrhotic livers. The data differentiating between tumors with portal vein distribution are interesting, but the difference is statistically not significant (table 2.12). The authors conclude that the post-mortem evidence suggests a lower likelihood of metastasis to the cirrhotic liver. There is apparently also no difference between Japanese and European patients (Seymour et al.) (fig.2.12). The rate has never been stated according to the cirrhosis Child-stage however.

Another state influencing the incidence of metastases, at least in colorectal cancer, is fatty liver. Defined as the finding on ultrasonography of the four factors, brightness, deep attenuation, increased hepatorenal contrast and vascular blurring, its presence apparently significantly inhibits the occurence of liver metastases, but not for metastases in other organs (Hayashi et al.) (table 2.13).

One hypothesis is that the portal blood flow is hindered by the thrombosis regularly present in cirrhosis, causing hypertension and some blood flow modification.

Table 2. 12 - Metastases to the Liver
Comparison of Cirrhotic and Non-cirrhotic patients
Literature Review of Seymour et al. 1999

	Cirrhotic N=1365	Non-cirrhotic N=33134
Overall Rate	23.7%	37.3%
Portal vein Tumors	29.8	47.6

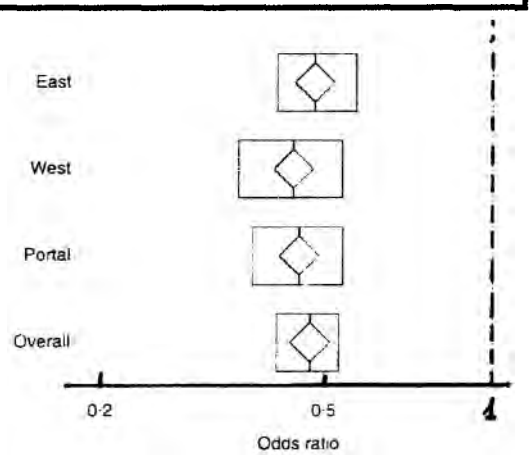

Fig.2.12 - Individual odds-ratios for different subsets of patients analyzed. The odds-ratio is at the central line, while the diamond size and the box give the 95% confidence limits (Seymour et al., with permission)

Table 2. 13 - Metastases to the Liver
Incidence in Fatty liver
Data of Hayashi et al.

	Fatty L. N=121	Non-fatty L. N=718	P
Liver	2/119 (1.6%)	115/603 (19%)	<0.001
Lung	40/81 (50%)	289/378 (76%)	0.035
Perit.	33/88 (37.5%)	215/452 (47.5%)	0.279

Another peculiar effect was noted by Utsunomiya et al. in hepatitis B or C virus infection, but it was not correlated with liver function tests. The presence of an infection significantly lowered the incidence of metastases, at least in colorectal cancer (table 2.14). This certainly needs confirmation.

Table 2.14 - Metastases to the Liver
Influence of Viral hepatitis infection
Data of Utsunomiya et al.

	Infected	Non-Infected	P
Liver	3/37 (8.1%)	85/401 (21.2%)	<0.05
Lung	2/37 (5.4%)	24/401 (6.0%)	NS
Periton	3/37 (8.1%)	40/401 (10%)	NS

One can conclude that several factors have an influence on the presence and development of metastases in the liver. The mechanisms are, however, unknown and somewhat hypothetical. Local biochemical and immunological factors can be invoked in analogy with other pathologies. It is likely that a study of the effects of various factors could aid to the understanding of the formation of metastases.

Symptoms

Nowadays, liver metastases are diagnosed in the presymptomatic stage by imaging methods at staging and at regular intervals during follow-up of the patient.

Symptomatology has been described in earlier series. Initially, virtually no patients with liver metastases do experience any symptom. Pyrexia of unknown origin or thrombo-embolic events without explanation may occur and be found to correlate a posteriori. The growth of the metastases can lead to hepatic or abdominal pain, depending on its location within the liver. The pain is more prevalent in fast-growing metastases due to distension of the liver (Glisson) capsule. Weight loss and metabolic symptoms may develop. Liver metastases in a posterior or superior region can irradiate pain to the right shoulder.

An enlarging liver coming down the costal arch is described as hepatomegaly, and indicates extensive liver disease.
In late phases, ascites, jaundice, portal hypertension signs and finally encephalopathy and precoma will develop. In fact, by the time clinical examination proves the presence of liver metastases, the proces is already at a relatively advanced stage. The modern development of imaging methods has certainly allowed an earlier diagnosis, though whether led to more efficient treatment is still an open question and one where the optimistic clinicians may be at variance with the more pessimistic ones.

Symptoms can be divided into presenting symptoms or complaints leading to a referral and the symptoms or signs then found at clinical examination (table 2.15). The symptoms of liver metastases can be divided into those related to the liver pathology, aspecific symptoms and symptoms related to the primary or other extrahepatic metastases, after which the liver meta-stases are then incidentally found.

Table 2.15 - Metastasis to the Liver
Clinical signs and symptoms in 81 patients
Data of Fenster et al. 1961

Liver abnormality (any)	95%	Portal hypertens	32%
Enlargement	89	Other (advanced)	20
Induration	77	Spider angiomas	9
Tenderness	64	Palmar erythema	10
Nodularity	53	Gynecomastia	2
Jaundice	27	Flapping tremor	1
Ascites	31	Fetor hepaticus	1

In the actual oncology textbooks, symptoms of liver metastases are no longer discussed, as almost all liver metastases are now found by imaging methods before any symptom occurs. We found it nevertheless interesting to mention the symptoms as they were presented several decades ago (table 2.16). As can be seen, signs are compatible with what is now considered advanced disease.
The manifestations of liver involvement, for example pain, tenderness, induration nodules and friction rub correlate with the degree of hepatomegaly. The incidence of ascites, fever and splenomegaly is independent of the degree of liver size (Fenster et al). The data will however vary somewhat according to the type of primary, as pancreatic and gallbladder cancer will lead more frequently to jaundice.

Table 2.16 - Signs and Symptoms of Metastasis to the Liver

	Fenster & Klatskin N=81, 1961		Weber et al. N= 404, 1972		VanWaes et al. N=166, 1976	
Sign	1st Compl.	Sympt	Compl.	Sympt	Referr.Sympt	Sign
Liver symptom	44%	67%	--	--	--	--
Hepatic pain	27%	36%	72%	--	32%	40%
Ascites	9	31	--	--	3	18
Jaundice	6	27	--	18	19	38
Abdominal mass	2	7	--	--	8	--
Edema low. extr.	--	--	13	--	--	--
Hepatomegaly	--	--	--	56	--	--
Splenomegaly	--	--	--	2	--	--
Primary or other M.	32	32	--	--	13	18
Non-specific complaints	23	95				
Fever	9	23	16	--	4	19
Weight loss	--	80	81	--	--	80
Anorexia	--	69	77	--	--	73
GIT symptom	--	62	19	--	--	--
Vomitus	--	--	17	--	--	--
General weakness	--	--	--	--	--	66

Ruptured Liver Metastases

Rarely, acute right upper quadrant pain and fever followed by acute abdominal syndrome can indicate rupture within the peritoneal cavity of a superficial metastases, similar to what can happen with a primary liver cancer. According to LaFlanza et al., up to 1999, 38 cases have been reported (table 2.17). It seems that kidney, bronchus and melanoma are the most frequent involved primaries, but 12 other primaries have been reported.

Table 2. 17 - Ruptured Liver Metastases
Reported cases and Primaries
Literature Review by LaFlanza et al. 1999

Nasopharynx	1	Testis	3
Bronchus	4	Breast	2
Stomach	2	Melanoma	6
Pancreas	3	Ovary	1
Gallbladder	1	Choriocarcinoma	2
Kidney	4	Cervix Uteri	1
Rectum-Colon	2	Lymphoma	1

The clinical picture of liver rupture, which is usually complicated by hemoperitoneum, varies from acute abdomen with pain in the upper right abdomen to unexplained blood loss and shock. Signs of peritoneal irritation, intraperitoneal-free blood on paracentesis, fever and leucocytosis may also be part of the presentation. Factors such as repeated manipulation, coughing and straining on defaecation have been implicated.

Imaging

The most widely used imaging method nowadays is transabdominal ultrasound. It is inexpensive and non-invasive and provides excellent screening results.
With current imaging technology, virtually all liver metastases 2 cm or larger and most of those sized 1-2 cm size will be detected, while only half of the nodules smaller than 1cm will be seen.
The aspect of the metastases varies somewhat with the primary involved. Metastases from gastro-intestinal and urogenital tract tumors are usually echogenic, but in the event of necrosis, they may be echo-free.
Breast and bronchial cancers, melanomas and lymphomas give echo-poor metastases, while mucin-secreting metastases such as those from colon and ovarian cancers may appear cystic.
Central necroses can give a target-appearance image.
The problem with US is that it rarely can detect small metastases and those located more posteriorly. Its sensitivity is lower than the other imaging methods.

The Color Doppler Perfusion Index (CDPI) has been a breakthrough in the detection. This index is the ratio of the hepatic arterial blood flow to the total blood flow. This method is supposed to have, according to some authors, a sensitivity of 100% and a specificity of 86 % for the detection of colorectal metastases. It would appear, however, that the measurement of CDPI is very operator-dependent, so that further studies are required.
Computer tomography is an excellent imaging method but its cost-benefit ratio is under discussion, certainly for routine use.
The metastases usually appear as low-attenuation areas after intravenous contrast enhancement.

In patients with a clinical suspicion of hypervascular lesions, the addition of unenhanced and arterial phase images is helpful. The uniphasic approach can characterize most of the lesions. Multiphasic scanning can however help in the differentiation of many, especially in the characterization of small lesions. Metastases are however always better visualized on enhanced scans.
As the cost of MRI decreases, it is increasingly being used as a primary imaging technique, supplying Tl and T2 signal information for the characterization of the focal lesions. It could perhaps best be reserved for equivocal CT-images (Sica et al.).
Magnetic Resonance Imaging may be used when ultrasonography and/or CT is not conclusive and when surgery is being considered. It undoubtedly provides better localization and definition of vascular invasion.

Haemorrhage can result in a more dense aspect and cystic appearance can occur in necrosis.

Table 2.18 - Hepatic Metastases
Structural Features on CT depending on Primary
Modified from Ferrozzi et al.

Calcified	Hypervascular	(Pseudo)-Cystic
GIT mucinous	Kidney	Ovarian carc.
Ovary serous	Carcinoid	Colon carcinoma
Ovary endometr	Colon adenocarc	Sarcoma
Osteosarcoma	Breast	Breast
Chondrosarc.	Melanoma	Bronchus
Islet cell tum	Islet cell tumor	Pancreas (exo)
Melanoma	Sarcoma	Gallbladder
Mesothelioma	Pheochromocyt	
Neuroblastoma		
Thyroid medullary		
Bronchus carc.		

Calcification within liver metastases is a well-known phenomenon. It is seen most frequently in metastases of primary mucinous adenocarcinomas and in colorectal cancer. It has also been described in ovarian cancer, breast cancer, renal cancer, thyroid especially medullary cancer and neuroblastoma (table 2.18).
Reviewing 230 CT studies of hepatic masses, Scatarige et al. found 28 or 12.2% with unequivocal calcifications. It was present in 9 of the 59 (15.3%) biopsy-proven HCC, and in 15 of the 82 (18.3%) from colorectal carcinomas.
The calcification is produced by the tumor itself or is a dystrophic calcification secondary to necrosis and/or hemorrhage within the tumor. At presentation of colorectal metastatic cancer, calcification was seen in 11% (Hale et al.). During treatment, 4% more develo-

ped calcification. The calcification can be peripheral, central or scattered throughout the lesion. The degree of calcification is also highly variable. This is discussed further in the chapter on metastases from colorectal cancers.

All imaging methods have the problem of low sensitivity for small nodules: that is those below 10 mm. These small nodules constitute the most important problem in the further evaluation of long-term survival and the decision wether to provide any 'adjuvant' treatment. In the next table (2.19), the differential possibilities of the different imaging methods is outlined, compared with another malignant condition (HCC).

Ways to enhancing sensitivity have been proposed by Dugdale et al. The technique is somewhat analogous to the detection of small hepatocellular carcinoma, based on the modifications of the blood flow that are evolving in small liver lesions. Hepatic metastases are associated with increased arterial perfusion and arterial phase enhancement. This is due to the exclusive arterial supply to the metastases (table 2.19).

According to the data from Schulz et al. discussed above, for each metastases seen, there is the possibility of missing at least one metastasis in colorectal cancers and four in the case of other malignant tumors. The detection of a small tumor within the liver parenchyme will depend on the one hand of the contrast C and on the other hand of the image noise N (Pistolesi et al.). This implies the need at imaging to enhance the liver parenchyme either positively or negatively, possibly even by utilizing adequate contrast media and timing of the image sequence, because of the hemodynamics of the metastases. This will differ according to size.

Hypovascular metastases, which receive a reduced arterial blood supply compared with the hepatic parenchyme will have a lower enhancement than of the liver parenchyme, also in the portal phase, which will show a negative contrast.

Small-sized metastases have an enhancement stronger than the hepatic tissue during the arterial phase. The larger hypervascular metastases receive arterial blood supply mainly from the periphery of the lesion, with a less perfused center. In the following phases, the center and the periphery will show the opposite behavior, resulting in a peripheral hypo-intensive halo.

Diagnosis

Nowadays, the diagnosis of liver metastases is almost never made on clinical grounds. Imaging methods are the mainstay as they are routinely done within staging procedures, when the primary is diagnosed or during the follow-up. It can of course be useful to do an ultrasonic or CT-guided FN biopsy to confirm the diagnosis in doubtful cases, but in most cases it is not mandatory.

The diagnosis of liver metastases with CT must be guided by the pattern of presentation of the lesion within the liver. The presence of other signs of metastatic disease in the neighbourhood will facilitate the diagnosis of malignancy. Several features can orient the diagnosis of liver metastases, although the variability of the image is quite great (Ferrozzi et al.) (table 2.20).

Table 2. 19 - Imaging Possibilities in the Differential Diagnosis between Metastases and Hepatocellular carcinoma (modified from Helmberger et al.1999)

Modality	Liver metastases	Hepatocellular carcinoma
Ultrasonography	Echo - poor or rich Echo - poor halo	Most echo-poor, difficult to outline
Doppler	very variable	hypervascularised, AV-shunts
CECT	hypodense, irregular, inhomogenous (without bleeding, necrosis)	irregular hypodense, irregular enhancement, paradoxal enhancement due to shunts
CTAP (') or CTA(")	due to necrosis, bleeding, peripheral enhancement possible	
Magnetic Resonance		
T1	most hypointense (bleeding, necrosis)	most hypointense (bleeding, necrosis)
T2	most hyperintense (bleeding, necrosis)	most hyperintense (bleeding, necrosis)
GdDTPA	in T1 like CECT	in T1 like CECT
SPIO(°)	no T2 enhancement, T1 possible (GRE°)	no T2 enhancement, but hyperintense
Nuclear		
colloid	as a cold zone	cold zone
HIDA	as a cold zone	uptake in about 50%
Blood pool	useless	defect on late images
Gallium	no uptake unless abcess or lymphoma	uptake in 90%
Angiography	hypovascular	hypervascular, shunts

CECT: Computer Tomography; CTAP: CT with arterioportography, CTA: CT with arteriography
SPIO: with super-paramagnetic iron oxide particles.

Table 2.20 - Primary Tumor, Aspect of Liver metastases at CT and Synchronous Pathology
Modified from Ferrozzi et al.,1999

Primary	Aspect of Liver Metastases	Synchronous Oncologic Pathology
Colon	Macronodular, Pseudocystic, hypodense Ring enhancement, hypervascular	Nodes para-aortic and mesenteric Ascites, peritoneal carcinomatosis Metastases in ovary, adrenals, lung
Stomach	Micronodular, hypodense, calcified Ring enhancement	Nodes celiac and gastrohepatic ligam. Ascites, peritoneal carcinomatosis Metastases in ovary, lung (lymph.carcin.)
Exocrine Pancreas	Micronodular, peripheral enhancement Pseudocystic	Nodes celiac, hepatic hilum, para-aortic Ascites, peritoneal carcinomatosis Metastases in adrenals, pleura, lungs
Endocrine Pancreas	Micronodular, hypervascular, Calcified	Nodes celiac, hepatic hilum, para-aortic Ascites, peritoneal carcinomatosis Metastases in adrenals, pleura, lungs
Bronchus	Macronodular, hypodense, pseudocystic Peripheral enhancement	Nodes hilar, mediastinal Metastases in adrenals, pleura, bone, brain, kidney
Gallbladder	Macronodular, hypodense, pseudocystic Peripheral enhancement	Nodes celiac, hepatic hilum, para-aortic Ascites, peritoneal carcinomatosis, lung
Melanoma	Micronodular, calcified, sometimes hemorrhagic	Metastases in spleen, lung, intestine, brain

CLASSIFICATION

In order to adequately compare various different treatment series, some classification systems have been propo-sed (Petrelli et al.):

Extent of involvement at laparotomy:
I <26% involvement
II 26-50% involvement
III >more than 50% involvement
Performance status
0 normal activity
1 with symptoms, but ambulatory
2 In bed less than 50% of the time
3 in bed more than 50% of the time
4 In bed whole time
Preoperative serum alkal.phosphatase
a less than 2x normal values
b between 2x and 4x the normal value
c more than 4x the normal value
Superscript
E with extrahepatic intraabdominal disease documented at lanarotomy
Example: III.3c

LIVER METASTASES of UNKNOWN PRIMARY

Liver metastases can present in patients as a first sign of an unknown neoplasm (type 1-metastases).
In reviews of these patients, it is helpful to know which are the most frequently involved primaries.
In the literature all patients presenting with any metastases anywhere are commonly grouped together without making distinction between sites, leading to erroneous conclusions. A patient with liver metastases from an unknown primary cannot be compared with a patient presenting with brain metastases from an unknown primary.

There are only a few series specifically addressing the patients presenting with liver metastases first. The best documented is the series from the MD Anderson Hospital published by Ayoub et al. dealing with 500 cases. They were extracted from a group of 1522 patients presenting with metastases of an unknown primary, or 32.2% (table 2.21). Data are not given according to gender, so that specific conclusions are impossible. Of all liver metastases of unknown primary, the primary was found in only 27%. One quarter of all primaries detected were supradiaphragmatic. In about half of the patients, there were other metastatic sites.

Table 2. 21 - Liver Metastases as first Sign
Primaries Involved (N=500)
Data of Ayoub et al. 1998

Primaries Found N=137, 135 patients

SupraDiaphragmatic (27.7%)			
Bronchus	25		
Breast	8		
Esophageal	5		
InfraDiaphragmatic (51%)		Not-Specified (21.1%)	
Stomach	7	Lymphoma	5
Colorectal	23	Melanoma	9
Pancreas	22	Sarcoma	4
Liver (')	13	Others	11
Kidney	5		

(') hepatoma or cholangiocarcinoma

Histologies in 365 Liver metastases with Unidentified

	Liver Meta Only		With other Site	
Adenocarcinoma	93	67%	129	57%
Carcinoma NOS	24	17	73	32
Neuroendocrine	18	14	15	7
Epidermoid	2	1	6	3
No pathology	2	1	3	1
TOTAL	139		226	

Based on an autopsy study of 2552 oncology patients, Basserman et al. mounted a probability scale for the primary eventually involved, depending on age and the metastatic sites. Although such data are not absolute, they are interesting as such, and give some idea of the repartition (fig.2.13 and 14).

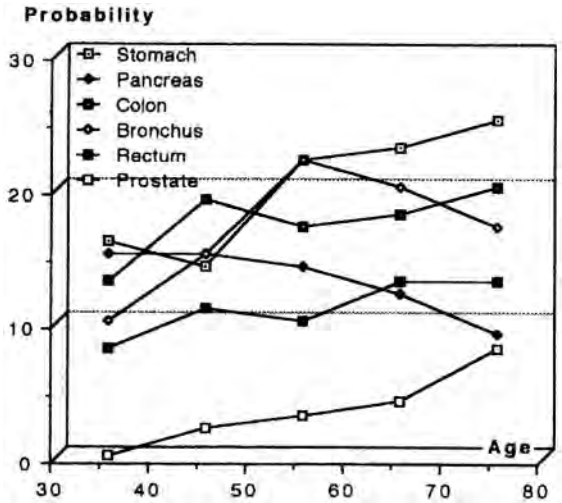

Fig.2. 13 - Probability of any primary tumor when liver metastases present in males, depending on age. (Drawn from data of Basserman et al.).

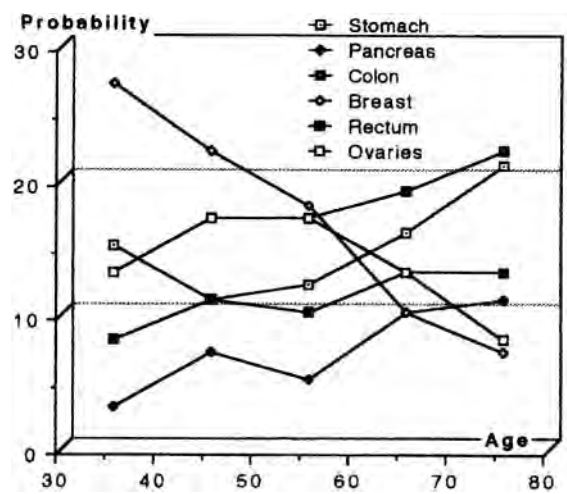

Fig.2.14 - Probability of any primary tumor when liver metastases present in females, depending on age. (Drawn from data of Basserman et al.).

METASTASES to the SPLEEN

Pathways

Metastatic cells can reach the spleen along three pathways

1. arteria splenica or the systemic way, including the anastomosal way short-circuiting the pulmonary and hepatic network, and giving rise to the solitary metastases;
2. the systemic way along the arteria splenica after passing through the pulmonary and hepatic network;
3. retrograd lymphatic flow which could explain secondaries from tumorous lesions close to the splenic hilus and as from the cardia.
4. retrograd flow in the splenic vein, anastomosing with different other intra-abdominal venous plexuses (fig.2.15).
5. Serosal implants from intra-peritoneal spread.

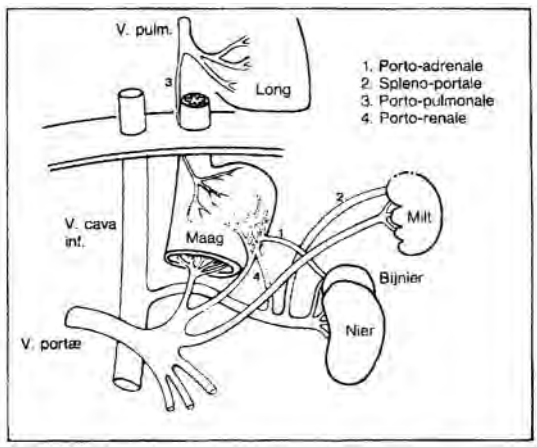

Fig .2.15 - Anastomotic venous plexus between stomach, kidney and spleen

Histologic evidence of metastasis resulting from retrograde lymphatic spread was proved in two cases involving a breast tumor and a common bile duct tumor by Goldberg et al.

Incidence

Metastases in the spleen escape clinical examination unless the spleen reaches a certain volume, but this will only confirm a splenomegaly. This explains why in earlier reports, spleen metastases were only detected

Table 2. 22 - Metastases to the Spleen
Incidence in autopsy series (type 4 metastases)

Author, Year	N	Frequency	Primaries
Harman 1948(')	116	12.9%	
Hirst 1952	2833	66 or 0.38%	melanoma 21.8% testis (hist?) 14.2 breast 6.9% ovary 5%
Nash 1966	544	16 or 2.9%	breast 9.7% colon 8.8% pancreas 5.4% rectum 4.0% lung 2.7%
Berge 1974	7165	312 or 7.1%	breast 12% ovary 12% skin 33% melan.?
Falk 1987	200	18 or 9%	breast 16% oatcell 20%

(') only 'advanced' cases

at autopsy (type 4), or less frequently in incidental surgical explorations. The data depend however on the type of patients coming to autopsy (type of hospital), but also on the autopsy study (table 2.22). In fact, splenic metastases are much more readily diagnosed, due to the more adequate imaging methods available, as earlier spleen was almpost out of reach.

Considering spleen-liver weight ratio, metastases are as common in both organs. Metastatic evidence is macroscopically seen in 60% (Berge), but at microscopy, metastases are seen either in the red or in the white pulp. Frequently it is restricted to the venous sinuses.

Breast tumors, bronchial cancers and melanoma are the most common primaries producing splenic metastases.

The most recent report and review of Lam et al. could retrieve 713 cases with splenic metastases from the literature (table 2.23). They report on a personal series of 92 patients in 12820 general autopsies or 0.6%. Of 1743 splenectomies, 1.1% were metastatic at pathology.

Table 2.23 - Metastases to the Spleen (N=713)
Primaries - Literature Review by Lam et al. (2000)

Abdominal Tumors		Supra-Diaphragmatic	
Colon Rectum	9.4%(“)	Breast	22.9%
Ovary(‘)	9.0	Bronchus	20.2
Stomach	6.9		
Pancreas	3.5		
Liver	2.7	Skin (Melanoma)	5.0
Kidney	1.8		
Prostate(‘)	3.6	Others	10.5
Urinary Bladder	1.7		
Cervix	2.8		

(“) of all patients with splenic metastases
(‘) gender distribution not stated.

Rare primaries found are nasopharyngeal, esophageal and choriocarcinomas (Lam et al.). Remark that intra-abdominal cancers are concerned in only half of the cases.

Only recently, a clinical series of 31 oncologic splenectomies has been reported (Lee et al.). The spleen was the only metastatic site in 8 or 26%. In 23 patients,an ovarian primary was concerned. The other primaries were colon (2), appendix (2) and endometrium, bronchus, peritoneum and a GI-stromal sarcoma, each one.

Pathology

Splenic metastases usually occur within two years after diagnosis of the primary. They are presumably observed more frequently at autopsy. Solitary metastases are exceedingly rare. A literature survey by Lam et al. disclosed 40 reported cases and concerns most often ovarian carcinoma.

The low frequency of splenic metastases when compared with hepatic, has given rise to several hypotheses. The tortuosity of the splenic artery and the immunological surveillance capability of the spleen are the most frequently cited. The absence of direct afferent lymphatics, the typical angulation of the splenic artery from its beginning at the celiac trunk and the ‘periodic’ contraction provided by the sinusoidal splenic architecture, possibly flushing out neoplastic cells, have also been advanced (Herbut et al.).

Based on the pathologic appearance of metastases within the spleen, Marymont et al. have analyzed 93 autopsy cases. The group consisted of 35 lung tumors, 18 breast cancers and 17 other different primaries. In 66% of the cases the metastasis was macroscopically visible, of which 90% were nodular. The group V type was the most frequent aspect and were only microscopically visible. The type of metastasis could not be correlated with the primary. It was noted however, that most of the diffuse types were caused by breast cancer, whereas almost all prostatic carcinomas (5/6) had only microscopic metastases (table 2.24).

Table 2. 24 - Metastases to the Spleen
Type and Location (Marymont et al. 1963)

Microscopic
Group I : in venous sinusoids only
Group II : in red pulp as microscopic nodules only
Group III : in white pulpas microscopic nodules only
Group IV : in trabecular vessel only
Group V : in several different elements of the spleen
Macroscopic
Group VI : nodular type
Group VII : diffuse type

With the modern imaging methods, they are detected earlier, so that their incidence during life is much better known.

In a series of 170 consecutive patients with splenomegaly, there were 59 due to lymphoma or a myelo-proliferative disease, and only 3 patients with metastatic splenomegaly, two from the pancreas and one from the stomach (O’Reilly).

During the last decades, a disproportionate number of solitary spleen metastases from gynecologic tumors have appeared in the literature, most of them incidental to abdominal CT survey.

The number of splenic metastases from bronchogenic carcinoma has risen to 5.6% (Kinoshita et al.).

Spleen weight correlated well with the pathologic aspects (table 2.25).

Table 2. 25 - Metastases to the Spleen
Pathology type and spleen weight
Data of Marymont et al. 1963

Microscopic (I to V)	163 gram (60-400
Tumor Nodules (VI)	236 gram (70-1100)
Diffuse Involvement (VII)	803 gram (100-3000)

Adenocarcinomas were the most frequent histology type in the series of Lam et al. (87/92). The meta-

stases could be identified macroscopically at autopsy in 80%, while the others were incidentally found at microscopy. The capsule was involved more than the parenchyma in 8 cases. The lesion was solitary in 31, multiple in 30, diffuse in 5. The spleen weight was more than 200 g in 25% of the patients. In all patients other metastatic sites were also noticed.

A distinction should be made between parenchymal and serosal, or capsular, implant-metastases. The latter are somewhat more frequent and are a sequella of an intraperitoneal spread.

Clinical Pattern

It is striking that Piekarski could detect at CT seven cases of splenic metastases without any visible hepatic involvement.
The splenic metastasis was symptomatic in only 7 of the 92 patients found with splenic metastases. Enlarging mass was found in 5 and ruptured in 2 (1 choriocarcinoma and 1 large cell bronchial cancer), as confirmed at laparotomy (Lam et al.).
Spontaneous rupture is a very rare presentation. Only 15 cases have been reported in the literature (Lam et al.). It should occur more frequently in men (9/15). Melanoma is a frequent primary.

Imaging

Plain film is an unreliable mode for visualizing the spleen. It can show splenomegaly with calcification. This i,s however, not relevant in the diagnosis of metastases. Indirect visualization can be done with a colon barium study.
The spleen can be visualized in its totality with nuclear scintigraphy. This still provides a sensitive and simple method for identifying structural and functional pathology. Simultaneous imaging of liver and spleen is obtained with ^{99m}Tc sulfur colloid, but heat damaged red blood cells labeled with ^{99m}Tc images the spleen alone. The technique with BMHP is now obsolete.
In the modern setting, ultrasonography is the first method of choice. It is easy to apply, cheap and non invasive.
According to Goerg et al., most (71/73 or 97%) non-lymphatic neoplasms are hypoechoic. Hyperechoic appearance was noted in one case of ovarian and one medullary carcinoma. This leads to the conclusion that any hyperechoic lesion is almost always a benign pathology.
The 'halo-sign' was noted in only three cases. This appearance has only been reported in specific cases. Calcifying metasases are somewhat specific to C-cell carcinoma, but otherwise there is no specific aspect of the echogenic image related to the type of primary.

At CT, the splenic metastases show as areas of decreased attenuation when compared within the surrounding parenchyma. Cyst-like metastases have been reported and some others only appear after contrast infusion (Piekarski et al.).

METASTASES to the PANCREAS

Pancreatic metastases are probably much more frequent than commonly appreciated. They are frequently 'buried' in a clinical syndrome of upper or widely diffuse abdpminal spread, hiding the diagnosis and infrequently a somewhat terminal situation. Nevertheless, solitary metastases resulting in a clearcut diagnosis are sometimes amenable to a rewarding and successful aggressive surgical treatment. In these circumstances, the diagnosis is important in order to correctly evaluate the particular situation.

Pathways

Several pathways may allow spread into the pancreas. Arterial spread is obvious for solitary metastases. Retrograd venous spread must be taken in account for cancers of the upper abdominal region. Invasion from peripancreatic and retroperitoneal lymph nodes and invasion from cancers of contiguous organs cannot be considered as a genuine pancreatic metastasis. These situations are commonly excluded in almost all reports.

Incidence

Data on the incidence are scarce and little there is are based on autopsy studies. The corresponding data of Willis and of Abrams are resp. 3% and 11.6% of the cancer patients.
From a series of 649 cancer patients without pancreatic or lymphomatous tumors, coming to autopsy, Matsukuma et al. retrieved 47 or 7.2% patients with pancreatic metastases.
For malignant melanoma figures of 37%, for breast cancer 19% and in bronchial cancer 9% have been reported (Diedrich et al.).

In a sizeable series of surgery of the pancreas, 2% of the pancreatic tumors removed were metastases from another primary (Roland et al.). Of 6,623 patients undergoing CT of the abdomen, 20 patients were found to have pancreatic metastases (Ferrozzi et al.).
It has been stated that pancreatic metastases are four times more frequent than primary carcinomas, but these are probably biased studies.

An approximative idea of the most frequent primary involved was obtained by analyzing the literature in two ways.
We first looked for some series, mainly radiological studies, who reviewed a number of patients with pancreatic metastases. The selected studies had at least 5 patients.The incident primaries are tabulated on table 2.26.

Table 2. 26 - Metastases to the Pancreas
Literature Data from series(')

Primary Involved			
Bronchus	50	Colon	11
Kidney	25	Ovary	5
Breast	14	Sarcoma	4
Stomach	14	Esophagus	3
Skin Melanoma	14	Uterus NOS	2

and additionally 1 case of
pleura, uterine sarcoma, melanoma of the eye, duodenum, salivary gland, prostate, gallbladder (NE), thyroid, cervix uteri, urachus, neuroblastoma, liver, oral, hypopharynx, unknown primary.

(')Rumancik 1984 (7 cases); Roland 1989 (27 cases); Didrich 1993 (19 cases); Boudghene 1994 (20 cases); Palazzo 1996 (7 cases); Ferrozzi 1997 (20 cases); Matsukuma 1997 (47 cases); Zgaggen 1998 (10 cases).

From these data we must infer that bronchial and kidney cancers are the most frequent origin of pancreatic metastases. We have to compare these data with the incidence rate at autopsy as was discussed previously for the different primaries.

A relatively large series was recently reported from the MayoClinics. Renal carcinoma accounted for 30% of the 66 cases, bronchogenic for 23% and 12% breast cancer (fig.2.15).

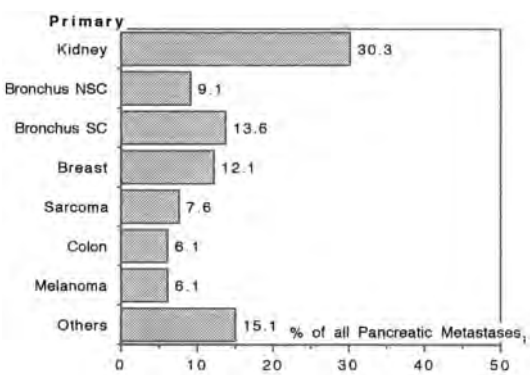

Fig. 2.15 - Distribution of primaries with metastases to the pancreas. (Redrawn from Klein et al.,)

A number of cases have been reported where the metastasis was the first sign of an unknown tumor (type 1 metastases).
A review of case reports in the literature shows that the distribution of the most frequent primaries cited is completely different. This can only be explained by the fact that for some tumors the appearance of metastases is somewhat unusual, either revealing or even very late in the evolution. Once again, literature studies will lead to incorrect conclusions.

Recently, LeBorgne et al. reported on 12 patients operated upon for one or more pancreatic or Valerian metastases. Five concerned a primary from the left kidney, while the others were 2 melanoma and one carcinoid, colon, breast, bronchial small cell and one venous leiomyosarcoma. In three, the diagnosis was simultaneous with the primary. In only two cases were the metastases multiple.

The particular vagaries of metastatic disease from the kidney will be outlined in the relevant chapter. The extreme variety in timing always brings the reporting author to the fact that this case is so particular and apparently worthy of a publication. Remark however that three cerebral tumors - glioblastoma, meningioma and a medulloblastoma - metastasized to the pancreas.
Our bibliometric analysis (table 2.27) reveals a high number of reports concerning kidney cancers, and fewer for colonic, but several other primaries are concerned.

Table 2. 27 - Metastases to the Pancreas
Literature data : case reports
collected by the author

Primary Involved			
Kidney	71 reports	Liver	2
Colon	2	Cervix Uteri	1
Bronchus	15	Head Neck	2
Breast	7	Heart	1
Sarcoma	7	Esophagus	1
Cerebral tumor	3	Thymoma	1
Melanoma	2	Thyroid	1
Carcinoid	2		

Interval

Rarely, pancreatic metastases have been reported preceding the diagnosis of a primary (type 1). The interval varies widely and can be very long, even several years after the treatment of the primary. The kidney cancers are a well-known example.
Specific data have been provided by Klein et al. (table 2.28). The longest (mean) interval was observed in renal cell carcinoma, 120 months or 10 years. In 9 of the 20 patients, it was even longer than 10 years. The long interval can render the diagnosis difficult, especially if patient does not mention previous surgery or other oncologic treatments.

Table 2. 28 - Metastases to the Pancreas
Interval according to the Primary
Data of Klein et al. 1998

Primary	Mean Interval	N after 60mo
Kidney	120 mo (9-295)	17 (85%)
Bronchus	9.1 mo (2-72)	1 (6.6%)
Small cell	5.7 mo (2-30)	none
Non small cell	14.2 mo (3-72)	1 (16.6%)
Breast	31.0 mo (1-101)	2 (25%)
Melanoma	78.2 mo (54-108)	2 (50%)

Pathology

The metastases are most frequently single.
It is, of course, necessary to differentiate the tumor from a primary pancreatic carcinoma.

According to Matsukuma et al, about 20% are purely ductal metastases, mimicking a primary cancer. The large ducts, either the main or secondary branches are involved, or medium-sized ducts.
Klein et al. identified 79 'tumors' in 66 patients, as metastases were solitary in 78.8%. They did not observe any particular preferential site within the pancreas. The majority (two-thirds) of the metastases appeared as tumors with discrete margins. Most of these were round with smooth borders, but some were lobular, while the others had indistinct margins (Klein et al.).

Symptoms

The symptoms of metastatic diseases within the pancreas are no different from a primary carcinoma.

Table 2.29 - Metastases to the Pancreas
Mode of Presentation

Asymptomatic
Late Onset Diabetes Mellitus
Icterus due to bile duct compression or invasion
Pancreatitis with or without icterus, with epigastric pain

As can be expected, epigastric pain is the most frequent complaint prompting the patient to seek advice and diagnosis. A more silent situation is jaundice, when the tumor obstructs the bile duct, and bleeding within the gastro-intestinal tract. In other cases the palpation of an abdominal mass, intestinal obstruction and unexplained weight loss have led to diagnosis in a number of cases (table 2.29).
Quite a number are asymptomatic. In 15 of 18 patients with pancreatic metastases, the diagnosis was obtained at routine follow-up imaging (Muranaka et al.).
Presentation as pancreatitis is not frequent, but when it presents thus it is usually related to breast cancer, skin melanoma and small cell carcinoma of the bronchus. Seven patients were reported by MacLatchie et al., with five from a stomachal cancer. High amylasemia, absence of alcohol abusus or biliary disease usually point towards metastasis, but in three cases the diagnosis was only obtained at surgery or autopsy. The metastatic invasion probably destroys small ducts, resulting in the release of pancreatic juice.

Table 2.30 - Metastases to the Pancreas
Factors to distinguish from pancreatitis
Modified from Mössner et al.

1. When there is a known primary, think of a metastasis
2. In the event of pancreatitis, exclude a metastasis
3. Primary pancreatic cancers can also present with pancreatitis
4. Some pancreatitis are paraneoplastic
5. In acute presentations, always exclude metastasis

A patient (M28) presented with a large mass in the retro-peritoneum, complicated with signs of acute pancreatitis. Several investigations were made without any specific diagnosis. Only at autopsy was a small nodule at the left testicle found to be a differentiated teratoma with embryonal carcinoma, the same as the retroperitoneal mass (Mössner et al.). The authors have stressed several ways to differentiate metastastic infiltration from true pancreatitis (table 2.30).

Imaging

If previously examination of the pancreas was almost out of reach, the advent of CT has revolutionized pancreatic exploration.
The pancreas is indeed well visualized with CT and their lesions can be detected on the basis of differential density or contrast enhancement to obtain better definition.
Pancreatic metastases have a variable enhancement pattern. In about 75% it is increased by 17% an uniform hyperattenuation. The enhancement is heterogenous in about half of the metastases with components of diminished attenuation. Entire hypoattenuation is observed in 20%. Some rare metastases have a cyst-like appearance and a few others have calcification.
Ductal obstruction is observed in one third, especially those located in the pancreatic head. Vascular involvement can be observed (Klein et al.).
Some features can help differentiate metastases from other pathologies, especially in the event of unknown primary (type 1 metastases).
Multiplicity of the lesions, coexisting metastases in the neighbourhood or elsewhere, a high degree of vascular perfusion are not typical of a pancreatic adenocarcinoma. Arterial encasement and calcification are much more common in pancreatic tumors.
It is more difficult to differentiate such tumors from a non-functioning pancreatic islet carcinoma.
It would appear that only the metastases from a renal cell carcinoma display some characteristic features such as a rapid enhancement during the early arterial and portal phase with adequate differential attenuation (Ng et al.), while in metastases from other primaries the features are much less characteristic at ultrasonography and CT (Biset et al.).

The CT characteristics have been discussed by Klein et al. The majority (75%) appear with discrete margins. They are usually round or ovoid with smooth borders or lobular. The pattern of enhancement is variable. Most have increased enhancement relative to normal parenchyme. In 60 % the enhancement is heterogenous and in 20 % it is entirely hypoattenuated, as in most cases of renal carcinoma.
Ductal obstruction was seen in 38%. Vascular involvement is rare.

In the few cases where the primary is not known at presentation, their multiplicity and coexisting other metastases in the neighbourhood are indicative of a metastatic proces. The high enhancement correlating

with hypervascularisation is a further indication. On the other hand, vascular encasement is much more common in primary cancers. A differential diagnosis with a non-functioning pancreatic islet carcinoma can be very difficult.

Diagnosis

As for many metastatic locations, the diagnosis is mainly based on presumption when a primary has been treated in the patient. Imaging studies play a key role in this situation, if needs be, supplied by FN aspiration biopsy or cytology. Biochemistry does not play an important role.
If the diagnosis of metastasis is not always evident at first sight, especially in patients who have been treated some years ago, a new primary in the pancreas cannot always be dismissed. In twelve patients treated for a non-pancreatic malignancy previously, the tumor was a metastasis in 5, but in the 7 others, it was a new primary of the pancreas (Whittington et al.).

METASTASES to the GALLBLADDER

Pathways

The hematogenous route is obviously the way metastatic cells will reach the gallbladder. Below the diaphragm, only the kidney and the stomach have been described as the primary source. Skin melanoma is the most frequent primary involved.
Direct extension is found in pancreas and liver cancer, while the latter can invade the gallbladder even through the lumen of the bile duct system.

Incidence

We found 36 references referring specifically to metastases in the gallbladder. The large majority concerned metastases from skin melanoma (18), but quite a number also from the kidney (9). Three were from a stomach cancer, two from a breast cancer, and one cervix uteri and one breast cancer.

Symptoms

The symptoms will be aspecific and very similar to cholecystitis and or biliary duct obstruction. Many are asymptomatic and found only at autopsy in conjunction with widespread abdominal metastases.
A rare presentation of gallbladder cancer is perforation of the tumorous wall with bile peritonitis. Only a few cases have been reported, such as the one of Shah et al. involving a patient with breast cancer.

Imaging

Presently, US-graphy plays an important role in the detection of pathology in the gallbladder, but the imaging features are not specific for a metastatic tumors. CT can probably better indicate the spread and infiltration in the gallbladder and neigh-bouring organs.
Four image patterns were discerned by Phillips et al. Pattern A shows a focal thickening with a metastatic deposit; B an intraluminal mass in a further normal bladder; C, is a combined A+B pattern and in D the gallbladder has been replaced by a large tumor. The different patterns represent in fact progressive stages. No specific pattern could be recognized in respect of the primary involved.

METASTASES to the BILE DUCT

The bile duct can be invaded either via its wall or from contiguous masses or lymph nodes with displacement. Both can result in obstruction and ensuing jaundice. This aspect has received relatively poor attention in the literature. Distinction between intraluminal metastases and extrinsic (nodal) compression is usually not made. The latter is most frequent for cancers of the neighbouring organs. Jaundice is the presenting sign in 70%, while pain is much less frequent, but is probably more frequent with intraluminal metastases. The mean interval between treatment of primary and diagnosis of metastases is 36 months.
The tumors associated with malignant biliary tract obstruction can be separated into two groups (Lokich et al.) (table 2.31). It can be seen that most primaries are intra-abdominal and that two-thirds of the metastases are in the common bile duct.

Table 2.31 - Malignant Biliary Tract Obstruction
Primary Tumors as Cause - Modified from Lokich et al.

Local Tumors		Distant tumors	
Pancreas	80%(‘)	Stomach	10-40%(“
Bile duct	5%	Colon cancer	20-30
Duodenum	1%	Breast cancer	10
Ampullar	1	Melanoma	15
		Other	1

(‘) of the local tumors causing
(“) of the secondary causes

Table 2.32 - Metastases to the Bile Ducts
Pathology Data from Thomas et al.

Primary		Site of metastases	
Colon	9cases	Common duct	18
Ri 6, left 3		Common hepatic	6
Gallbladder	5	Bifurcation	3
Melanomas	3	Hepatic	3
Pancreas	3		
Small bowel	3		
Breast	2		
Stomach	2		
Ovary	2		
Lymphoma	1		

From the files of one hospital, Thomas et al. were able to report on 30 cases. Their relevant data are

shown in table 2.32. Several case reports on colonic cancers, even of the revealing type, have been reported later.
Percutaneous transhepatic cholangiography or ERCP now together with CT are the diagnostic imaging methods.

Icterus through Metastases

Icterus (jaundice) is a common symptom in daily practice. Rarely is it caused by metastatic processes. There may however be different anatomic causes (table 2.33). Ultrasonography, CT and ERCP are useful in the diagnosis of the anatomic site, but clinical judgment of the obtained images is important.

Table 2.33 - Icterus through Metastases
Anatomic Sites

Hepatic
- Intrabiliary metastases
- Metastases in lymphatic channels of the portal tract
- Widespread (miliary) hepatic metastases

Extrahepatic
- Nodal or tumoral mass with extrinsic compression of hepatic or choledocal duct
- Metastatic masses at head of pancreas
- Retroperitoneal metastasis from germinal, pelvic or renal tumors

METASTASES to the ADRENAL

The adrenal glands are a frequent site of metastases. Decades ago, they were usually overlooked, as imaging modalities could not visualize them. They were almost always only detected at autopsy. With the advent of CT, however, this has changed dramatically, as adre-nal metastases can now be detected at staging.

Pathways

With the exception of invasion through a neighbouring renal cancer or rarely by retroperitoneal lymph nodes, metastases in the adrenal are invariably hematogenous.
The arterial supply to the glands comes from three major feeding vessels (fig.2.16). The superior adrenal artery arises from the inferior phrenic artery, the middle artery comes directly from the aorta while the inferior artery is a branch of the renal artery. These trunks give off numerous small branches before entering the gland. They resemble the teeth of a comb as they arise from the major adrenal arteries.
There is, however, only a single vein draining each gland. On the right side, the vein enters the inferior vena cava directly. On the left side, it joins the inferior phrenic vein before emptying into the left renal vein (Dunnick).

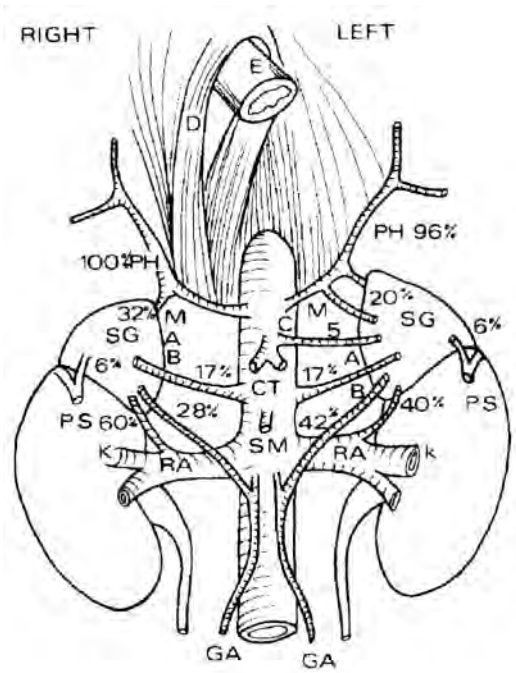

Fig.2.16 - Diagram of the blood supply of the suprarenal glands. Incidence of vessels in 25 cases shown in percentages. (E: esophagus, D: diaphragm, SG: suprarenal gland, K: kidney, CT: celiac trunk, MS: superior mesenteric artery, U: ureter, PH: phrenic artery, C: celiac branch, AB: aortic branches, RA: renal artery,PS: superior polar art., GA: gonadal art., M: middle art. from the phrenic art. (Bianchi et al. , with permission)

Incidence

Previously, precise data on incidence were only available from autopsy series. The rate varies from 10 to 60%, depending on the primary concerned (table 2.34).

Table 2. 34 - Metastases to the Adrenal
Overall literature data from autopsy series

Primary	Involvement (%)
Bronchial cancer	30-60%
Breast cancer	35-60%
Mal.Skin Melanoma	40-60%
GI tract cancer	10-20%
Renal cell cancer	40-50%

In the early literature, Sahagian-Edwards et al. found 354 patients with adrenal metastases in 9,582 autopsies or 3.7%. Bilateral invasion was seen in 40% of these. In 806 consecutive autopsies, Meyer et al. found macroscopic metastases in 294 or 36%, with only 17 bilateral involvement.
The classical series of Abrams et al. reported on 270 or 27% adrenal metastases in 1,000 oncology patients (Sherry et al.). An autopsy study of 91 oncology patients disclosed adrenal metastases in 31%, of which 78% were bilateral. Of the 30 bronchial cancers 56% had adrenal metastases (Bellaggia et al.).

Recent autopsy data have been provided by Saeger et al. In all cases with known malignancy, 45 or 19% were found to have adrenal metastases. Although numbers are not large, breast, bronchus and colon carcinoma have proportionally the highest incidence (table 2.35).

Table 2. 35 - Metastases to the Adrenal
Autopsy data by Saeger et al. 1998

Primary	N	Adrenal Meta
Colorectal	39	6 (25.6%)
Bronchus	34	10 (29.5%)
Stomach	30	3(10.0%)
Prostate	22	6 (26.0%)
Breast	13	5 (38.5%)
Urinary Bladder	11	2 (18.0%)
Ovary	9	2 (22.2%)
Liver	8	1 (12.5%)
(Lymphomas)	14	1 (7.1%)
Kidney	4	0
Malignant Melanoma(skin)	4	0
Uterine Cervix	3	2 (66.6%)
Others	13	0
Total	234	45 (19%)

Modern staging procedures have now added clinical data.

Fine needle aspiration cytology or biopsy in patients in whom an adrenal nodule is detected on CT will confirm the metastatic nature. These will partly be due to incidentalomas, but not in the patients known to have had a malignant tumor treated before. Katz et al. reported on 9 cases, all with different metastatic locations. In 4 patients the primary was not detected, whereas all others were bronchial cancers of different histologies, stressing the high incidence of these metastases in bronchial cancer (see Chapter 8).

Of 50 adrenal masses, 23 were metastatic malignancies with 14 or 30% of bronchial cancer (Wadih et al.). From the 23 there were 5 metastases of an unknown but subsequently found malignancy (typel metastases): breast, prostate, pancreas, lymphoma and one still unknown.

Table 2.36 - Metastases to the Adrenal
Surgical series N=52, Data of Lo et al. 1996

Primary		Histology	
Kidney (°)	15	Adenocarcinoma	36
Bronchus	11	Large Cell carc	5
Colon	7	Melanoma	3
Unknown (')	5	Sarcoma	3
Melanoma	3	Small cell carc	2
Stomach	3	Transitional	2
Urinary Bladder	2	Squamous Cell	1
Leiomyosarc Uter	2		
Breast, prostate,	1		
Gallbladder	1		
Mal.Fibr.Hist.	1		

(°) in 9 contralateral
(') 4 Adenocarcinoma, 1 Squamous Cell

Based on CT appearance, an adrenal mass was found in 45 oncology patients. A fine needle aspiration revealed metastases in 22 or about half. Almost all masses larger than 3cm yielded a positive finding (Candel et al.).

Similar data were reported by Dusenbery in 54 masses and Saboorian in 188 patients.

A series of 52 patients submitted to adrenalectomy for metastatic disease was reported by Lo et al, from the Mayo Clinics. Four patients had bilateral metastases. Although certainly biased towards operability, the list of the primaries probably parallels the global relative incidence (table 2.36). This series demonstrates that adenocarcinoma is the most frequent histology type seen as metastasis within the adrenal, at least in this operative series.

Pathology

The rich blood supply to the adrenal sinusoids is an important factor in the high incidence of metastases. It has been claimed that the high corticosteroid level within the gland favors the development of metastases, but this has never been proved.

Metastases are seen either in the medulla or in the cortical zone. Almost no study has evaluated the differential distribution.

In his extensive classical autopsy study, Willis reported that small metastatic emboli most frequently occur in the cortical capillaries. Some authors have pointed out that the state of the adrenals at autopsy is important for the interpretation, as the glands rapidly undergo autolysis after death. The difference in cellular aspects between normal and cancerous tissue is not always evident, in view of the cellular morphological variation.

One important fact is that both adrenals are involved in 50 to 60 % of the cases in most series.

Logically, metastases should involve both sides equally. Some authors have reported on a predilection for the left side. Fourteen of 16 palliatively treated patients had left-sided, all bronchial cancers (Soften et al.). In their studies on esophageal and stomachal cancers, Cedermark et al. observed more metastases in the left adrenal. One hypothesis is that the left gland is larger and has a richer arterial blood supply.

Hemorrhagic adrenal metastases have been described, mainly in bronchial cancer. Flank pain in 3 patients was the revealing sign of a metastatic adrenal mass from an unknown bronchial cancer (Shah et al.). These authors found 6 other cases in the literature, with one from a gastric cancer. The clinical presentation varies and will depend on the intensity of the hemorrhage, but it is mostly sudden and intense pain that brings it to the attention. It is indeed a rare presentation, but like most of the metastases probably seriously underreported. Adrenal hemorrhage is encountered however in many other pathologies.

If adrenal metastases are solitary, a curative resection

could be indicated. However such a condition is not frequent. Kim et al. have reported on 37 operated patients. The condition was encountered in 17 bronchial cancer (table 2.37).

Table 2. 37 - Metastases to the Adrenal
Primary with solitary adrenal metastases
Patients operated and reported on by Kim et al. 1998

Bronchus	17	Esophagus, germ cell,
Renal cell	9	Melanoma, Bladder,
Colorectal	5	Collecting duct, Unknown, 1

It is striking that 27/37 or 73% were asymptomatic. Another particularity is the high incidence of kidney metastases when the adrenal is involved (Cedermark et al.).
Autopsy studies have stressed that adrenal metastases are a relatively late appearing aspect of the systemic metastases. It is quite evident that the incidence of adrenal metastases increases with the number of other metastases, but the chance of adrenal spread increases with the distance between the studied metastatic site and the primary tumor (Cedermark et al.).
Specific problems encountered for particular primaries are discussed in the relevant chapters (Part 2).

Symptoms

Adrenal metastases have been known to be a cause of Addison's disease since he first described his syndrome first in 1855. Of his 11 cases, four were due to metastatic disease.
Since then, numerous cases of Addisonian crisis have been reported, complicating and even revealing (type 1-metastases) the metastatic process: 2 cases (1 bronchus and one lymphoma) by Sherry et al. and 2 other bronchial cancers by Kung et al. However, about 90% of the adrenal tissue must have been destroyed before this syndrome occurs.
A more extensive survey was performed by Seidenwurm et al. In the radiology files they found 21 adrenal metastases in 6,000 CT reports, with 4 or 19% with typical Addisonian problems. At the same hospital, they found in 949 autopsy reports 35 patients with adrenal metastases of which 3 or 8.6% with addisonian problems. Additionally, 1 case was retrieved from the endocrine consultation files.
Adrenal insufficiency is probably more frequent than generally accepted, as the symptoms of insufficiency are probably masked by the downhill course of these patients with widespread metastases.
A literature review in 1983 (Goldenberg et al.) disclosed that of the 16 cases reported, 12 were from a bronchial cancer. A later review in 1987 disclosed 27 cases, of which 18 or 66% were from bronchial cancer. Other primaries were breast, stomach, seminoma and pancreas (Kennedy et al.).

Why should this condition be rare? Four possible reasons have been proposed by Hill et al., as quoted by Cedermark et al.:

1. The similarity between an Addison-crisis and symptoms of disseminated metastatic process.
2. Treatment with glucosteroids is often offered to these patients, masking the hypo-adrenalism that might be present.
3. Diagnostic procedures are often omitted in this situation, possibly precluding the detection of metastasis.
4. The remaining adrenal tissue can become hypertrophic in compensation for a limited destruction.

Pain in the back and/or upper abdomen is common when the metastases are symptomatic. This is probably a sign of fast grow and large metastases. Invasion of the neighbouring kidney is frequent in these situation. The pain will either correlate with relative fast-growing metastases or less frequently with a hemorrhage.
As adrenal hemorrhage as such is not uncommon, only 10% of this situation is probably due to metastases, sometimes even as a revealing sign (Outwater et al.).
Recently, Lutz et al. reported a comparative study in general symptomatology comparing oncology-patients with and without adrenal metastases (table 2.38). Symptoms of adrenal insufficiency seem to be present in several patients with or without adrenal metastases, but they are more frequently due to the underlying malignancy than to a relative glucocorticoid deficit.

Table 2..38 - Metastases to the Adrenal
Symptomatology - Data of Lutz et al.

Symptom	No Meta. N=11	Unilater N=8	Bilater N=9
Weakness	27%	75%	56%
Fatigue	9	25	22
Anorexia	27	63	67
Nausea-Vomiting	18	38	22
Weight loss	9	50	56
Hypotension	9	--	33
Electrolyte dist.	--	--	11
Hyperpigmentation	--	--	--

Imaging

Asymptomatic metastases are presently detected by imaging methods at staging and during follow-up. This has revealed that

- many, esp. bronchial cancers, have adrenal metastases at diagnosis;
- in quite a number, these metastases are solitary leading to the possibility of 'curative' surgery;
- not all detected adrenal masses are metastases and pose a diagnostic problem (see further).

Technology has revolutionized adrenal imaging in the last decades, as these organs could hardly be visualized before.

Table 2.39 - Comparative image characteristics of the different tumoral conditions of the Adrenal (Falke)

	Metastases	Pheochromocytoma	Non.Funct.Adenoma	Adrenocort. carc.
Dimension	Large variation	Large variation	Small <3.5cm	Mostly >5-6cm
Image	Inhomogenous	Large variation	Homogenous	Inhomogenous
Morphology	Irregular margin	Large variation	Smoothly marginated	Irregular margin
CT-density	Soft tissue	Soft tissue	Low 'fat' density	Soft tissue density <10H.U.
MRI	Intermediary Int. T2 in 75%	High signal on T2	Isointense = liver(T2)	Interm.int.on T2
Contrast	Substantial enhancement	Significant enhancement	No or almost no enhancement	Substantial enhancement
Localisation	Often bilateral	---	Often multiple,unil- or bilateral >50% local invasion No increase in FU>1yr.	

H.U.: Hounsfield units; FU: follow-up

Table 2.40 - Imaging features allowing a differential diagnosis for Adrenal Masses

Pathology	Plain CT	Postcontrast CT	T1-weighted	T2-weighted
Normal	Homogenous	Enhancement		
Adrenal Carcinoma	Inhomogenous	Irregular enhancement	Iso-intense	2+bright
Metastases	Homogenous	Enhancement variable	Iso-intense	2+bright
Myelolipoma	Hypodense	No enhancement	Bright	Dark
Hemorrhage	Hyperdense	No enhancement	Bright	Bright
Adenoma	Homogenous	Enhancement	Iso-intense	Iso-intense
Pheochromocytoma	---	---	Iso-intense	4+bright

Ultrasonic imaging is the technique of choice for screening. When a suprarenal mass is seen, it must be ascertained of wether it is renal or adrenal. A demonstration of margin makes it likely to be of the adrenal, while this is not evident for renal masses.
The enlarging of an adrenal mass will displace the kidney inferiorly and the upper pole rotates posteriorly and laterally, a characteristic finding in large adrenal masses (Forsythe et al.).
The internal structure of the adrenal must also be evaluated, as many metastases are inhomogenous due to necrotic and/or hemorrhagic zones (table 2.40).

CT is the method of choice. It relies on the presence of fat in benign lesions, resulting in low densities.
Metastases are usually large in size, inhomogenous due to necrotic and/or hemorrhagic zones. The margins are irregular. In fact no characteristic CT finding can be defined. Some are large, other small. Most are sharply marginated, round and equal numbers are homogenous or heterogenous. Many adrenal masses invade the upper pole of the kidney (Cranston et al.).
Metastases have usually an increased intensity on T2W images at MRI, but the method does not add significantly to the workup so that adrenal biopsy is indicated when non-conclusive results are obtained.
While all lesions with a CT density reading above 20H are malignant and none benign, quite a number of meta-static lesions have a reading between 0 and 20H. The same can be said when size is used as cuttof. No benign lesion is larger than 3 cm, but some malignant ones are smaller.

Chemical shift-imaging, with adrenal signal normalized to that of the spleen (adrenal-spleen ratio, ASR) can help to differentiate.
When ASR was less than 70, all lesions were benign and all those with ASR above 75 were malignant. Between 70 and 75, the result was variable, but the correlation with CT-H-reading could adequately delineate (MacNicholson et al.).

More comparative data, useful for differential diagnostic purposes, are on table 2.39.

Diagnosis

If adrenal masses are found at staging and signs or symptoms are absent, it is mandatory to determine their nature. As many adrenal metastases are asymptomatic or silent, diagnosis now rests on imaging and the cytologic or bioptic confirmation. This is, in fact, unnecessary and superfluous in the presence of multiple other metastases, as this will not change the treatment policy in respect of the patient.

Nuclear medicine has not received the attention it deserves in adrenal diagnosis. Nevertheless many studies have outlined the possibilities of an adequate study. The principle is that a normal adrenal will show uptake of the nuclide, as NP-59 (iodine-131-6-iodomethyl-19-norcholesterol), while a 'destroyed' one will not. An enlarged adrenal showing uptake, called concordant (with an abnormality on other imaging studies) is almost certainly an adenoma.

When there is no uptake, a tumor, primary or secondary, is most probable (Francis et al.).

Cytology offers a good and relatively easy way to diagnosis, despite being invasive, and has with a very low complication rate. In spite of its oncologic importance, this is hardly discussed in the classical oncology-pathology textbooks.
The correct placement of the needle is critical. An important cytology criterion (Saboorian et al.) is the presence of benign cortical cells, typically with a low nuclear/cytoplasmic ratio and pale, lipid-laden cytoplasm. As these cells have a fragile cytoplasm, the resulting naked nuclei may resemble metastatic small cell carcinomas. One must look for intact cortical cells, which show a more regular chromatin, without hyperchromasia, nuclear pleomorphism, necrosis or apoptosis as is usual in undifferentiated carcinomas. Differential diagnosis with hepatic and renal cells should also be considered (Saboorian et al.).
In any case, this method is a valuable tool in the diagnosis, with a high specificity and accuracy. The diagnostic accuracy of CT-guided FNAB is better than 90% in several series.

Biochemistry

The literature is quite silent on specific blood biochemistry in patients with adrenal metastases. Some authors have studied a very limited number of patients, though without coming to noteworthy conclusions.
Biochemical screening does not seem relevant as levels of plasma cortisol hormones, dexamethasone tests, ACTH and catecholamines are not different from patients without metastases. Only when more than 80-90% of the adrenal has been destroyed, values of adrenal insufficiency can be found, as has been discussed above.
Recently however, Lutz et al. have compared 17 oncology patients with adrenal metastases to 11 others without adrenal metastases (table 2.41).

Table 2.41 - Metastases to the Adrenal Gland
Biochemstry- Data of Lutz et al.

	N	Cortisol in nmol/L Baseline	Stimulation (‘)
No Adrennal Meta	11	307+33.2	794.6+41.2
Unilateral Metast.	8	440+53.5	990.8+92.9
Bilateral Metast.	9	637+92.1	1151.4+155.5
		P=0.04	P=0.03

(‘) 60 min. after ACTH 250 microgr.1-24

In patients with adrenal metastases, higher cortisol values are found, probably to maintain homeostasis due to activation of the hypothalamic-pituitary-adrenal axis. The authors define it as a subclinical adrenal insufficiency with a shift in adrenal steroidogenesis from mineralocorticoid secretion towards glucocorticoid secretion, as found usually in patients with critical illness. This suggests an impairment of the function of the zona glomerulosa in tumor patients.

Peculiar Situation

Low serum sodium, high renin and low aldosterone were the biochemical signs of a patient experiencing blackout spells and episodes of giddiness. Hypoadrenalism was suspected and adrenal metastases of a bronchial epidermoid carcinoma were found in a 56-year old man (Taylor et al.).

Bibliometry

To the extent that the number of reports specifically concerning metastases in the adrenal gives an idea of the incidence of the primary concerned, we found that kidney and bronchus carcinoma have the highest number (table 2.42).

Table 2. 42 - Metastases to the Adrenal
Primary concerned - Review by the author

Breast Cancer	7 reports	Skin Melanoma	2
Bronchial Cancer	40	Stomach	4
Colon-Rectum	6	Prostate	3
Endometrium	1	Sarcoma	1
Esophagus	2	Thyroid	3
Kidney	49	Testicle	1
Liver cancer	16	Urinary Bladder	1

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Caution: References are given for documentary purposes. Not all have been reviewed or used in the redaction of the text. We do not claim completeness of data. The references are as much as possible grouped per subject heading.

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3
METASTASES to the DIGESTIVE TRACT

Metastases in the gastro-intestinal tract are an insidious pathology in oncology, because of their aspecific symptoms. They carry a poor prognosis, mainly because many are asymptomatic and acute symptoms as hemorrhages and obstruction can lead to death of the patient.

Autopsy studies have shown that about two thirds of the oncology patients are asymptomatic and metastases will go unnoticed to the patient and to the clinician alike. They are another proof that many tumoral processes kill patients without any signal, or get lost and overshadowed by other clinically more symptomatic metastatic problems.

Based on 288 autopsies, excluding lymphomatous and intra-abdominal cancers, the incidence of metastases in the gastro-intestinal tract amounted to 7 percent of the oncology patients examined. Malignant melanoma is responsible for about 30%, while for all others it oscillates between 4 and 8%. Bronchial and mammary cancer are the most frequent primaries involved (Telerman et al.). A noteworthy fact is that two-thirds of the metastatic involvements were unnoticed before death (table 3.1). Similar data were obtained in a endoscopy series by Kadakia et al.

Table 3.1 - Metastases to the Digestive Tract (N=28) Autopsy data by Telerman et al.

Primary	N	with GITmeta	Percent
Bronchus	134	10	7.4%
Breast	72	3	4.1
Head-Neck	43	2	4.6
Melanoma	19	6	31.5
Other	20	1	5.0
Total	288	22	7.6

We will in turn discuss the metastases in the esophagus, the stomach, the duodenum, the small intestine, the appendix, the colon, the rectum, in the anus and specifically those in the peritoneum and the mesenterium

METASTASES to the ESOPHAGUS

Pathways

As is the case with many organs, one has to consider separately hematogenous arterial spread and invasion from neighbouring organ cancer or even mediastinal lymph nodes have to be looked at separately. Contiguous invasion seems to be twice as frequent as hematogenous.
Vascular spread to the esophagus can be either arterial or venous. It has been stated that the seeding from intra-abdominal tumors occurs via the para-esophageal vessels and lymphatics and for breast cancer via the mammary-intercostal-azygos system (Nussbaum).
The first type with intramural and submucosal spread (fig.3.1) occurs mainly in cancer of the pharynx and larynx, thyroid, bronchus and stomach. These true blood-borne metastases are the rarest event. Of the 62 cases reported by Agha, the authors noted direct spread in 28 (45.2%), nodal spread or invasion in 22 (35.5%) and hematogenous spread in 12 or 19.3%. Unfortunatedly, they did not separate the primaries according to this type of spread.

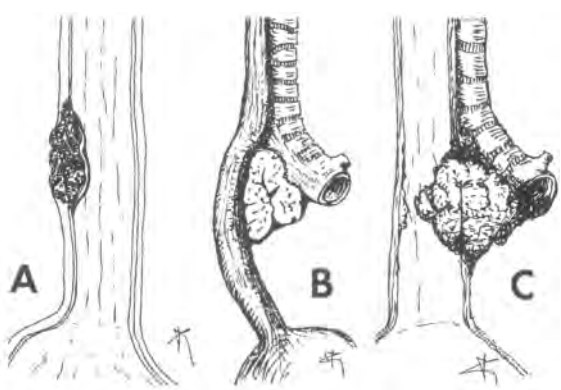

Fig.3.1 - The three modes of involvement of the esophagus by a metastatic process: (A) intramural and submucous (B) extrinsic compression due to a mediastinal 'tumor' (C) invasion through a bronchial tumor

Incidence

Metastases to the esophagus are rarely reported. The first report was from Gross and Freemand in 1942.
A literature review by Garusi in 1969 could find 82 cases to which they added 4 of their own files. In an autopsy study reported in 1944 on 599 cancer patients, 1.3% had esophageal metastases and 3% had esophageal invasion from an extra-esophageal tumor (Toresen).

Table 3.2 - Metastases to the Esophagus 1885-1969
Literature data (series of Garusi and of Nussbaum)

Primary Site	N	Primary Site	N
Breast	28	Kidney	1
Pharynx	26	Prostate	1
Stomach	10	Testis	1
Skin (')	5	Bone	1
Bronchus	5	Tonsil	1
Larynx	4	Lymphoma	1
Liver	1	Unknown	1

(') not stated if melanoma

Needless to say, a second primary of the esophagus has to be taken in account for H&N carcinomas.
More recent statistics were reported by Washington et al. in 1995 (table 3.3).

Table 3.3 - Metastases to the Esophagus
Literature review by Washington et al. 1995

Primary	Literature	Own cases	
		Surg	Autopsy
Melanoma	8	2	0
Bronchus	24	0	9
Breast	25	0	1
Prostate	-	0	0
Germcell Tu	1	0	0
Colon	0	0	0
Pancreas	0	0	0
Gynecologic	-	0	1
Kidney	1	0	1
Unknown	0	0	1

Table 3.4 - Metastases to the Esophagus
Autopsy data from NCCHospital, Tokyo(1979-1988)
Data of Mizobuchi et al.

Primary	N	Esoph.Meta	
Bronchus	450	51 (34)	11.3%
Breast	188	14 (10)	7.4
Stomach	326	13 (9)	4.0
Cervix Uteri	117	8 (9)	6.8
Tongue	51	5 (2)	9.8
Liver	170	4 (3)	2.4
Ovary	40	1 (1)	2.5
Others	682	16 (12)	2.3
ALL	2024(')	112 (76)	5.5%

(x) in parenthesis the cases with microscopic metastases
(') the number is higher than the number of autopsies, as 161 had double and 14 had triple cancers.

In 1,835 oncology-autopsies at the National Cancer Center Hospital in Tokyo metastases in the esophagus were found in 112 patients or an incidence of 6.1%. In 67.8% of them, the metastasis was only detected at microscopy, demonstrating that esophageal metastases are more frequent than usually admitted on clinical grounds (Mizobuchi et al.).
The macroscopic incidence in this series is 36/1835 or 2%, well in agreement with previously reported data.
While bronchial carcinoma is the primary most often concerned, the incidence of esophageal metastases is also the highest for this tumor. It should be noted however that the authors did not separate con-tiguous from distant invasion and considered these as lymphatic metastases. The incidence per primary is given in table 3.4.

Pathology

The metastases will usually be located in the middle third or less commonly the lower part. The esophageal involvement is usually over a short segment, but a long narrowed segment or intraluminal filling defects have also been reported.
Secondary esophageal involvement when it is from an infradiaphragmatic tumor, is usually accompanied by prominent mediastinal invasion as can be seen on conventional chest film. Thoracal or breast tumors involve the esophagus without mediastinal pathology being visible on chest films (Anderson et al.).
Of 112 autopsy cases, the metastases were visible in 36 and only at microscopy in the others.The diffuse infiltrative type was the most frequent (20/36), a protuding type in 11 and as an ulceration in 5 (Mizobuchi et al.). The same authors report a case where the esophageal metastases presented first and the bronchial tumor was seen only at surgery.

Interval

There is a remarkable difference in interval between diagnosis of the primary and occurence of the metastasis: ranging from relatively short periods for bronchial cancers to 5 to 7 years for breast cancer.
Type 1 metastases have been reported however for bronchial cancers.

Symptoms

Dysphagia is present in only half of the patients (Toreson). Most cases in which the involvement was found at autopsy, were asymptomatic (Holyoke).
A literature review by Caramella et al. on 47 cases confirmed dysphagia as the chief complaint. While the symptoms are not specific, the clinician should be aware of the possibility.

A very rare situation due to metastasis is achalazia, dysphagia for both solids and liquids, with regurgitation, chest pain and aspiration. The few reported cases (table 3.6), were shown to have high gastric invasion with extension towards the cardia and extensive perineural invasion of the esophagus, with-

out any significant tumoral invasion or obstruction. Most are gastric cancers, but cases from pancreatic, prostatic and bronchogenic cancers have been reported (Eaves et al.).

Table 3.5 - Metastases to the Esophagus
Symptoms (N=47)
Literature review by Caramella et al. 1983

Dysphagia	47.0%
Bleeding	4.2%
Weight loss	23.4%
No symptoms	8.5%

Reporting on 7 patients, Tucker et al. established three clinical criteria that characterize the secondary achalazia: advanced age (>50 yrs), symptoms less than one year and a marked weight loss (more than 15 pounds).

The description in the case of Shulze et al. is typical: a hyperemic mucosa and thickened wall at endoscopy, with at microscopy a mucosa displaced by an adenocarcinoma. At the cardia, the tumor infiltrated through the muscularis and even reached the attached striated diaphragmatic muscle.

Table 3. 6 - Metastases to the Esophagus
Cases reported with secondary Achalazia

Author	Patient	Primary Tumor
Kolodny 1968	F46	Stomach Adenocarcinoma
Shulze 1975	M49	Stomach
Tucker 1978	F71	Stomach Adenocarcinoma
Tucker 1978	F66	Bronchus Oat cell
Tucker 1978	M83	Pancreas Adenocarcinoma
Tucker 1978	M32	Stomach Adenocarcinoma
Tucker 1978	M56	Stomach Adenocarcinoma
Tucker 1978	F79	Stomach Adenocarcinoma
Tucker 1978	M63	Stomach Adenocarcinoma
Sandler 1982	?54	Stomach Adenocarcinoma
Sandler 1982	?74	Stomach Adenocarcinoma
Roark 1983		Hepatocellular Carcinoma
Eaves 2000	M75	Prostate Adenocarcinoma
Maroy 1988	F40	Breast cancer

Imaging

As already mentioned, mediastinal widening is common on chest films in cases of esophageal involvement.
Barium swallow studies usually show smooth concentric strictures or indentation of the esophagus. Achalasia-like pictures have been described. The radiological literature is quite silent on this problem. This is quite understandable, in view of the rarity of the occurence.
The radiological features are clearly dependent on the type of spread. The contiguous organ involvement is indistinguishable from a primary esophageal tumor, but the presence of an adjacent tumor mass will direct the diagnosis. The mediastinal nodes will show nodular indentation, compression, deviations and segmental narrowing.
Real hematogenous metastases will pose a diagnostic challenge, as they usually show short strictures with normal or minimally irregular mucosa.
Differential diagnosis with primary carcinoma is obvious (Agha).

Diagnosis

Actually, most should be diagnosed by the esophagoscope, but as the tumors are most frequently intramucosal, no ulceration will be seen, making biopsy unpractical and frequently negative (Phadke et al.).
If biopsy is generally diagnostic in esophageal carcinoma, it can be negative in the event of secondary involvement, as the cancer is submucosal.
When bougienage is attempted, many lesions perforated, probably due to the secondary friability of the wall (Atkins et al.).

METASTASES to the STOMACH

Metastases to the stomach are not commonly reported. The complaints are aspecific and in oncology patients the symptoms will probably be disregarded as symptoms due to other widespread metastases or secondary to the various treatments. Endoscopy is now more frequently performed, but reports on metastases are still rare.

Pathways

Here too, a distinction has to be made for secondary invasion from neighbouring cancers, as from the pancreas, the liver or the transverse colon. The distinction is not always made in the reported series.

The two most important ways of dissemination are arterial and spread along the mesenteric attachments.
When the deposits are located in the submucosal layer the hematogenous spread will create nodular lesions, with desmoplastic response. This can remain intramural but can also become intraluminal or subserosal and ulcerate. This is the main pattern seen with melanomas and bronchial cancer.
Infiltrative growth like that of a linitis plastica and respecting the mucosal layer, is often encountered with breast cancer.

The spread along mesenteric attachments especially in the region of the gastrocolic ligaments between the transverse colon and the greater curvature is an invasion per continuitatem. Another example is direct invasion from the pancreas.
Lymphatic spread with involvement of the upper stomach from a left lower lobe bronchial carcinoma has also been described.

Incidence

In 31541 autopsies of patients who died at the London Hospital (all oncologic?), Higgins found 64 patients with secondaries in the stomach, of which 21 were from bronchial cancer patients.

Metastases in the stomach are rare. Caremella et al. could retrieve 249 cases from the literature up to 1983. This would represent only 0.36% of autopsy cases of cancer patients, but Caramella et al. found involvement in 23.3%. In a series of 1951 necropsies of non-hematological malignancies, Green et al. found 57 patients with gastric metastases.

Table 3.7 - Metastases to the Stomach
Autopsy data of the NCCH, Tokyo 1982
Data of Saitoh et al.

Primary	N	N meta	Percent
Esophagus	340	43	12.6%
M.Melanoma	26	8	30.8
Tongue	21	3	14.2
Thyroid	32	3	9.4
Breast	276	21	7.6
Lung(Bronchus)	628	29	4.6
Uterus	270	9	3.3
Miscellaneous	3493	61	1.7
Total	5086	177	3.5

Of these, 51 were men reflecting the population of a Veteran Administration Center. The same authors mention the incidence of 10 cases diagnosed in 260 gastric endoscopy biopsies. Autopsy data will more or less reflect the population treated and depend on the type of hospital concerned. Saitoh reported data from the National Cancer Center Hospital (NCCH) in Tokyo, showing that there esophageal cancer is the most frequent primary (table 3.7). This of course raises the problem of a simultaneous new primary.

Unfortunately, the data are not given according to gender. Nevertheless, they reflect very well the propensity according to the primary, where again malignant melanoma scores high. The most frequent primary encountered giving rise to gastric metastases in the series of Green (89% men) is bronchial carcinoma (table 3.8). When patients from oncology institutes are concerned, breast cancer and melanoma also score frequently.

Table 3.8 - Metastases to the Stomach
Primary tumors leading to (review of Green 1990)
Autopsy series (four literature series)

Tumor	Number	%	Tumor	N	%
Bronchus	68	30.2	Pancreas	15	6.6
Breast	26	11.5	Liver	11	4.8
Melanoma	27	12.0	GI tract	17	7.5
Testis	9	4.0	Various	9	12.8
Thyroid	6	2.6	Ovary	8	3.5
Cervix	9	4.0	Total	225	

Total N autopsies: 61,887 + (N? of Willis)

In their report, Washington et al. compared their files with the literature data and found comparable data (table 3.9). It is a striking fact that more gastric metastases are found at autopsy than during clinical evolution.

Schmidt reported on two cases of bronchial cancer and reviewed the relevant literature. The metastatic rate from this tumor varies between 2 and 7% (table 3.10).

Table 3.9 - Metastases to the Stomach
Literature review by Washington et al. 1995

Primary	Literature	Own cases	
		Surg	Autopsy
Melanoma	132	6	3
Bronchus	95	0	5
Breast	152	0	6
Prostate	1	0	0
Germcell Tu	11	0	1
Colon	5	1	1
Pancreas	7	0	1
Esophagus	42	0	0
Liver	2	0	0
Kidney	8	0	0
Skin	1	0	0
Head and Neck	2	0	0
Thyroid	5	0	0
Bladder	0	0	1
Gynecology	0	0	3
Other	-	0	3
Total	463	7	25

Table 3.10 - Gastric metastases from Bronchial Cancer
Literature data by Schmidt et al. 1989

Author	N	% GI meta	%Gastric meta
Ochsner 1942	3047	4.3%	no data
Higgins 1962	911	--	2.3%
Burbige 1980	147	12.0%	7.0%
Antler 1982	423	14.0	2.4%

The leading primaries are melanoma in both genders, bronchogenic cancer in men and breast cancer in women. It appears that 10-20% of all melanoma patients develop gastric metastases. Small cell bronchus carcinoma is the most usual histology type and lobular carcinoma for breast cancer, resulting in an overall frequency of 2 to 15% of the autopsy cases. Some authors have discerned a higher incidence in the last decades, probably explained by the longer survival of the treated patients, allowing time for metastases to develop.

The incidence at endoscopy in a Cancer Center has been reported by Bognel et al. From 12,012 endoscopies, they isolated 17 metastastic cases or only 0.14%, 9 being male patients with 5 melanomas, 2 kidney, 1 rectal and one pharyngeal tumor. Of the 8 female patients, 5 had a breast cancer.

The time interval between diagnosis of the primary and the gastric metastases is almost never stated. Only Saito et al. mention a large variation in 13 cases: from 4 synchronous or type 2 metastases up to 5 years in a breast cancer patient.

As far as the location in the stomach is concerned, we found only data for breast cancer provided by Taal et al. from 237 patients. Several regions were simultaneously affected: 21 lesions were in the antrum, 20 in the corpus, 8 in the cardia and 8 in the fundus. Additionally, 8 lesions were present in the duodenum.

Pathology

There are three main morphological types of lesions:
- multiple nodules of varying size with tip ulceration arising on the crest of normal rugae,
- submucosal tumor mass elevated and ulcerated at the top, giving a volcano-like aspect,
- non-ulcerated masses.

Polyps, flat ulcers and plaques are rarely described, but might well be an early manifestation. Linitis plastica infiltration is commonly described in cases of lobular breast cancers.

Linitis plastica refers to a diffusely infiltrating carcinoma in a hollow organ, mainly of the digestive tract, resulting in a rigid and somewhat thickened wall with preservation of the shape and lumen. At histology, there is diffuse infiltration of the submucosa and muscularis, but multiple nodular metastases can complicate the picture. At radiology, it is undistinguishable from the primary stomachal linitis plastica.

Symptoms

As can expected, there are no specific symtoms that could reveal gastric metastases. They consist of gastric complaints such as epigastric pain, nausea and vomiting and sometimes hematemesis and perforation.

A literature review by Caramella et al. of 115 cases stresses the frequency of abdominal pain and weight loss, but shows that about one third were symptom-free (table 3.11).

Of 57 autopsy cases, 30 or only 53% had GIT symptoms (table 3.12).

Table 3.11 - Metastases to the Stomach
Symptoms in 115 cases
Literature review by Caramella et al. 1983

Symptom	
Dysphagia	6.1%
Bleeding	26.9%
Abdominal pain	33.0%
Acute obstruction	7.8%
Weight loss	27.8%
Mass palpable	4.3%
No Symptom	34.8%

In a review of the literature in 1983, the most frequent symptom was occult or overt bleeding and a chronic occlusion syndrome with pain (Caramella et al.). Almost 35% were asymptomatic and found only at autopsy, acute symptoms were rare and infrequent: and acute occlusion 7.8%, hematemesis 5.2%. A mass palpable on clinical examination was present in only 4.3%.

Table 3.12 - Metastases to the Stomach
Symptomatology Data of Green 1990

Symptom	Endosc. N=10	Autopsy N=30
Abdominal pain	8	27%
Nausea and vomiting	3	27%
Guiac positive stools	3	47%
GIT bleeding	2	53%

Diagnosis

The modern mainstay of diagnosis is gastroscopy. The endoscopic aspects have been described by a number of authors. The lesion can be either solitary or multiple, erosive, ulcerative or nodular. An almost pathognomonic aspect is the multiplicity of the lesions (table 3.13). The ulcerative aspect is also somewhat different from the classic peptic ulcer. Moreover endoscopy allows biopsy for a more pertinent diagnosis.

Table 3.13 - Metastases to the Stomach
Endoscopic aspects (Green 1990)

At inspection		
Multiple	33/67(')	(49%)
Single	34/67	(51%)
(') autopsy and endoscopy cases		
At autopsy		
Ulcerated	44/57	(77%)
Raised submucosal	13	(23%)
Single nodule	8	(62%)
Multiple	5	(38%)

The endoscopic features of gastric metastases were reviewed in 22 patients by Taal et al. (table 3.14).

Table 3.14 - Metastases to the Stomach
Endoscopic aspects in 22 patients (breast cancer)
Modified from Taal et al. 1992

Macroscopic aspect			
Linitis plastica	8	Cardiac stenosis	3
Extrinsic tumor	4	Pyloric stenosis	1
Multiple nodules	1	Benign ulcer	1
Malignant ulcer	4		

Endoscopic US-graphy allows a more detailed study of the gastric wall. Small submucosal lesions can be revealed, where the mucosa would appear normal under standard endoscopic studies. A number of authors have established criteria of gastric linitis (Lorimier et al.):

1. rigidity of the gastric wall;
2. a wall thickness exceeding 6mm;
3. enlargement of the second and third layers, with a thickness of the second layer exceeding that of the fourth layer;
4. a poor demarcation between the different layers.

Radiology has previously played an important role. Several different images have been described, including ulcerated intraluminal or intramural lesions,

especially suspect when multiple. A peculiarity is the large ulceration compared with the diameter of the tumor, while the surrounding mucosa appears normal. Non-ulcerative formations either intramural or intraluminal are generally multiple but not frequent.
While no particular image can be correlated with a distinct primary, the rare subserosal form is usually associated with an infiltrating colon transverse lesion. Multiple bulls'eye images will however evoke metastases from malignant melanoma, while linitis plastica images are seen in about 50% of the gastric metastases from a breast cancer and will suggest a diagnosis of breast cancer (Menuck et al.).

METASTASES to the DUODENUM

The duodenum is a rare site for metastases, but this is probably underreported, as it lies near organs frequently involved in tumoral processes. Most of the cases are grouped in publications dealing with intestinal metastases.

Pathways

Metastases reported in the duodenum can be of different types (fig.3.2).
The hematogenous type is the least frequent.
Invasion from nearby metastatic para-aortic lymph nodes is common and frequently described (fig.3.3). Invasion from contiguous cancers from the colon, the pancreas, the gallbladder and the right kidney has been also reported. Several cases of duodenal involvement have been reported as first and late signs of renal cancers. To this can be added the invasion from peritoneal (trans-coelomic) seedings from ovarian and colonic cancers.
Another not infrequent situation is intramucosal spread along lymphatics from cancer of the stomach (intra-mural metastases).

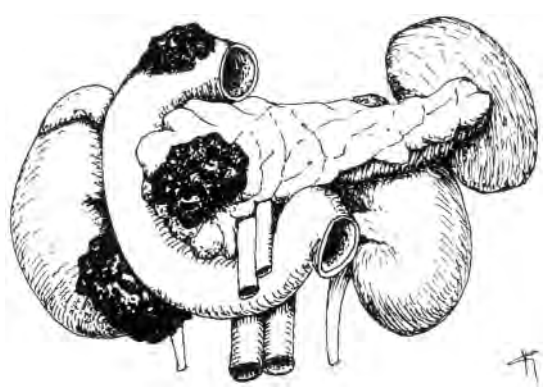

Fig.3.2 - The different ways of metastasis to or invasion of the duodenum

Incidence

As reports are scanty, incidence is hard to evaluate. From a series of 425 with an abnormal radiology of the small intestine, Smith et al. were able to find 33 patients with metastatic processes in the small intestine, of which 11 were in the duodenum.
Six were in the descending, 3 in the third and 2 in the fourth part, including the ligament of Treitz.
As primaries are listed mixed with the jejunum and ileum, the primaries to the duodenum cannot be individualized. However, the authors state that about all duodenal metastatic situations in the descending part were of the contiguous or lymphogenic type, from invading tumors of the adjacent right colon and kidney and also from retroperitoneal or nodal enlargement.

Fig.3.3 - Impending invasion of the duodenum from a retroperitoneal para-aortic lymph node mass

Table 3.15 - Metastases to the Duodenum (') Series of Veen et al. 1976

Colon	5	Esophagus	1
Kidney	2	Corpus Uteri	1
Pancreas	2	Melanoma	2
Gallbladder	1		

(') contiguous invasion without widespread metastases, excluding extensions of obvious cancers in neighboring organs.

Table 3.16 - Metastases to the Duodenum Literature Review by Washington 1995

Primary	Literature	Own cases	
		Surg	Autopsy
Melanoma	30	1	0
Bronchus	1	1	1
Breast	13	0	0
Germ Cell Tumor	4	--	--
Kidney	5	0	0
Sarcoma	1	--	--
Skin	1	--	--
'Gynecologic'	--	0	2
Urin.Bladder	--	0	1
Colon	--	0	1

In an early report by Ngan, 3 of the four cases were from metastatic lymph nodes (cervix uteri and two testis) and possibily one from an ovarian carcinoma

caused by peritoneal nodules.
A series of 14 patients was reported by Veen et al. The primaries are listed on table 3.15 and one can remark that most were probably contiguous invasion. The two melanoma cases are almost certainly hematogenous.Another series of 13 cases has been reported by Lämmli et al. They clearly separate the hematogenic from the nodal type and do not consider contiguous invasion. There were six of the first, four malignant melanomas, one pancreas and one small cell bronchus carcinoma. All others were invaded by metastatic retroperitoneal nodes from testis (3) tumors, one ovarian and one uterine tumor and two renal tumors

Table 3.17 - Metastases to the Duodenum
Primaries
Series of Minardi et al. 1998

Colon	5
Pancreas	5
Kidney	2
Ovarium	1
Bronchus	1
Unknown	1

The literature review by Washington et al. including the cases is listed in table 3.16. It is not clear which criteria have been applied but strictly hematogenous metastases are apparenly very rare.The most recent report was published by Minardi et al. in 1998. Of 44 patients diagnosed with metastases in the small intestine, 15 (or 34%) were at the duodenum (table 3.17).
A series of fifteen cases of contiguous invasion of the duodenum were reported by Altorfer et al. Gallbladder cancer was the primary in 8, with three colonic (right angle), 1 bile duct and 1 renal cancer. Two retroperitoneal masses of unspecified origin were the last two.

Timing

A number of metastases in the duodenum of type 1-(revealing) have been reported, mainly for breast and kidney cancers. Some have been reported several years after treatment of the primary, also mainly for breast and kidney carcinoma.

Pathology

Only Lämmli has described the macroscopic aspects of the duodenal metastases. They are either polypous or ulcerated-polypous. No other report addressing this aspect has been found.

Symptoms

Weight loss, obstructional symptoms and epigastric pain are probably the first, although some are asymptomatic.
A few reports mention hematemesis as the first symptom. This is presumably frequent when lymph nodes break through (Lämmli et al.), but is also a frequent sign in metastatic renal cancer.

Diagnosis

Imaging with barium can show discrete or multiple filling defects, alterations of the mucosal pattern, stenosis or displacement of the duodenum (Ngan). The classic 'bull's eye' image is also mentioned, but like all images, they are aspecific.
At present gastro-duodenoscopy is probably the mainstay for diagnosis, together with CT, but reports are lacking. Arteriography would delineate the extent of the tumor, but CT is probably sufficient.
More details on duodenal involvement will be discussed in the chapters dealing the different primaries (Part 2).

METASTASES to the SMALL INTESTINE

Pathways

Excluding direct invasion, three modes of dissemination can be discerned:

1. Direct invasion by a non-contiguous primary along the fascias or mesenteric attachments or by lymphatic permeation.

The first occurs when the carcinoma breaks down the different fascia normally separating the intestine from the organs and then spread along the mesentery. It usually concerns a pelvic carcinoma such as ovary or uterus.

Lymphatic blockage in the involved nodal chains causes lymphatic reflux resulting in neoplastic emboli.

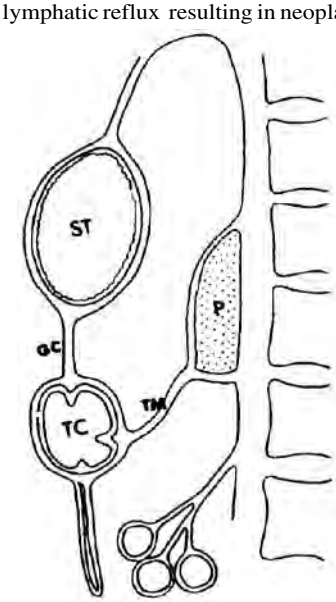

Fig. 3.4 - Sagittal view of the peritoneal reflections including the stomach, the pancreas and the transverse colon. The gastrocolic (GC) inserts superiorly and the transverse mesocolon postero-inferiorly (Meyers et al.)

2. Dissemination by the peritoneal fluid (ascites).
   As described by DeCastro and later by Myers, the primary cancer breaks through the peritoneal cavity and then creates deposits along the pathways of intraperitoneal fluid flow. The preferred locations are the pouch of Douglas, the terminal portion of the mesentery, the sigmoid mesocolon and the right paracolic gutter.
3. Hematogenous spread (Caramella et al.).
   Metastases form in the submucosa, and create polypoid formations, often multiple and intraluminal. This is frequent in malignant melanoma, breast and bronchial cancer.

Incidence

It would appear that the majority of metastatic cases are from pelvic carcinomas. The frequency is however very difficult to evaluate, as generalized involvement is also hard to differentiate from direct invasion.
Hematogenous spread is certain for malignant melanomas, where 25 to 35% of the cases have intestinal metastases diagnosed in vivo.
A series of 14 patients with intestinal metastases not resulting from direct extension was reported by Farmer et al. It concerned four malignant melanomas, 5 from the cervix uteri, 3 from the colon and one ovary and bronchus each. One metastasis revealed at surgery an asymptomatic tumor of the colon. Eight cases involved the ileum, in 3 the jejunum, and both in 3.

In the series of Minardi et al. concerning intestinal tumors, 50% were metastatic.
From the literature review by Washington et al., melanoma and gynecologic tumors would appear to be the most frequent primaries involved (table 3.18).

Table 3.18 - Metastases to the Small Intestine (N= 369)
Literature Review by Washington 1995

Primary	Literature	Own cases	
		Surg	Autopsy
Melanoma	242	11	3
Bronchus	44	3	7
Breast	48	3	6
Germ Cell Tu	1	0	2
Pancreas	--	0	8
Kidney	11	1	2
Skin	1	0	0
'Gynecologic'	5	11	11
Prostate	--	0	1
Urinar.Bladder	--	3	2
Head Neck	2	0	0
Thyroid	2	--	--
Colon	3	8	4
Stomach	10	--	--
Liver	--	0	1
Other G I	--	1	4
Sarcoma	--	0	1
Unknown P.	--	2	2

Pathology

As shown in fig.3.5, any metastatic embol within the submucosa can either evolve to a polypoid tumor or a progressive ulceration of the mucosa.
Farmer et al. were able to identify at resection three principal types in non-contiguous metastases:
1. spherical mesenteric masses encroaching on/or extending into the intestine. It was encountered particularly in gynecologic tumors.
2. intramural masses frequently with ulceration, not specific for a particular primary.
3. bulky polypoid masses extending into the lumen, sometimes surprisingly bulky and mainly encountered in malignant melanoma.

Table 3.19 - Metastases to the Small Intestine
Radiology series of Myers et al. (N=107) (1972)

Invasion from contig.tumor		Embolic	
Stomach	9	Melanoma	23
Transv.Colon	6	Breast	10
Pancreas	5	Bronchus	7
Invasion fr.non-contig.tumor		Seeding	
Ovary	6	Ovary	14
Uterus	4	Pancreas	7
Prostate	3	Stomach	6
Kidney	3	Colon	3
		Uterus	1

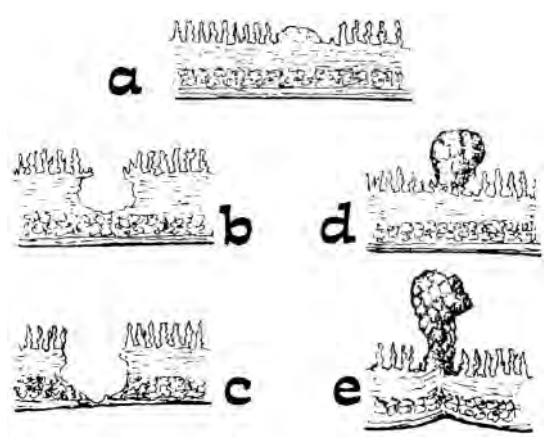

Fig.3.5 - Metastases in the Small Intestine - Relationship of metastatic growth to the four coats of the intestine.
(a) young metastasis situated in the submucosa; (b) ulcerated growth involving muscle; (c) ulcerated growth extending through muscle and infiltrating subserous tissues; (d) pedunculated metastasis involving only the mucous and submucous coats; (e) a pedunculated metastasis adherent to and producing invagination by traction of muscular coat, an incipient intussusception (Willis)

Analyzing their 107 radiological cases, Meyers et al. clearly separated the patients according to the metastatic mechanism (table 3.19). Three types of intestinal metastases can be distinguished, as shown on fig.3.6: the intramucosal embolic, the intramural and the serosal resulting from any peritoneal spread.

Symptoms

Due to the differences in the material reported the symptomatology will vary somewhat, but as can be expected, abdominal cramps or pain, due to obstructive lesions are the most frequent cited.
A literature review by Caramella et al. on 354 cases reveals that bleeding is quite common as first sign. About one fifth comes to diagnosis because of intestinal obstruction (table 3.20).

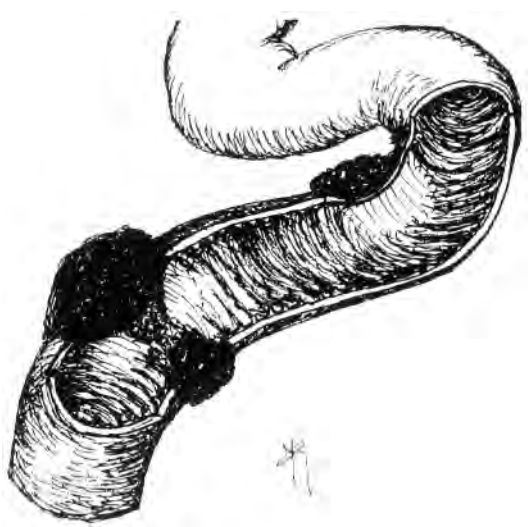

Fig.3.6 - The three different type of metastasis within the small intestine.

Perforation and intussusception are mentioned in several case reports, as well as acute hemorrhage. Intussusception is frequent, especially for malignant melanoma. Shiraishi et al. reported on a series of 4 cases, two from small-cell carcinoma, one from a cervix uteri cancer and one from a pleural mesothelioma.

Reviewing 27 cases of intussusception at their hospital over a period of 10 years, Eisen et al. remarked that metastatic disease was the cause of an intussusception in 8/22 or 36% of cases. No specific primary could be remarked, although 2 were from a lymphoma and 3 from a melanoma. One was from a sarcoma and two others from a bronchial cancer.

Table 3.20 - Metastases to the Small Intestine
Symptoms in 354 cases
Literature review by Caramella et al. 1983

Symptom	
Bleeding	36.7%
Abdominal pain	15.8%
Chronic obstruction	18.6%
Acute obstruction	21.7%
Weight loss	37.0%
Mass palpable	3.1%
No Symptoms	9.9%

Diagnosis

Radiological studies with barium were for a long time the standard method of examination when there was suspicion of intestinal involvement.
Awareness, clinical evaluation and CT are the keys towards the diagnosis. In oncology patients, differential diagnosis with sequellae of treatment, either steroids, radiation, cytostatic drugs or previous surgery, is mandatory (Koury et al.).
Radiology findings in intestinal metastasestake several forms (Smith et al.).
Intramural involvement with thickened, somewhat flattened mucosal folds, with evidence of transversal stretch is common. Annular constriction can appear as further desmoplastic involvement.
Mesenteric and/or peritoneal involvement is usually associated and visible as stretching and fixation of mucosal folds transverse to the longitutinal axis of the lumen. This is due to adhesion of small bowel loops to a tumor mass.
Evidence of ulceration is not frequent but can appear as a deep ulceration, polypoid nodule or cavitation of a large mass. The desmoplastic reaction and sclerosis with adherence of the bowel to the tumor mass can then lead to angulation or sharp kinking.
Necrosis of a tumor mass can cause fistulas from the intestine to other organs such as colon or to other segments. Extrinsic compression is observed when masses grow in the mesenterium or in adjacent segments. Intra-luminal outgrowth, although rare, can cause intussusception.

METASTASES to the APPENDIX

Pathways

Coelomic invasion is usually common in patients with ovarian carcinoma. Metastases from extra-abdominal tumors are most probably hematogenous.

Incidence

Metastasis to the appendix is a rare event. In 196, Latchis et al.could find only 11 cases in the literature to which they added one case from a breast cancer (table 3.21). Five were found at autopsy or celiotomy, the eight others presented with acute appendicitis. Perforation was present in 5 patients.

Table 3. 21 - Metastasis to the Appendix
Literature review by Latchis et al. 1966

Breast	4	Colon	1
Stomach	2	Ovary	1
Bronchus	2	Kidney	1
Pancreas	1		

Symptoms

The symptoms, if present, are not different from the 'usual' appendicitis, which may be complicated by perforation and peritonitis. Many are probably asymptomatic

Imaging

A few reports on sonographic examinations of masses at the appendix have been published. There are no specific features allowing a diagnosis a primary or secondary tumor and differentiate it with other appendiceal pathologies.

Diagnosis

The final diagnosis is the histology of the resected appendix.

METASTASES to the COLON

Metastases in the colon are relatively infrequent, but probably mostly undetected.

Pathways

The secondary involvement from other abdominal or pelvic neoplasms is either hematogenic, but more frequently specific pathways are taken along the peritoneal and mesenterial folds (Krestin et al.) (fig.3.7)

Cells from tumors of the pelvis can spread via the greater omentum towards the colon between the taenia omentalis and taenia libera. Tumors of the stomach will extend along the gastrocolic ligamentum between the taenia omentalis and the taenia mesocoloica, while those from the pancreas will extend between taenia mesocolica and taenia libera. The reverse is true for colonic cancer, depending on the site of the tumor (Krestin et al.).

Incidence

Myers states that breast cancer is the principal primary source of colonic metastases, but gives no data.
Of 3,569 patients with breast cancer, 17 were found to have colonic metastases (Taal et al.) after examination for abdominal complaints.
In fact, all parts of the colon can be committed and lesions are usually multiple (table 3.22).

Table 3.22 - Metastases to Colon from breast cancer Series of Taal et al. N= 17 (1992) (several patients had multiple lesions)

Cecum	3	Descendens	7
Ascendens	9	Sigmoid	9
Transverse	10	Rectum	7

Pathology

It first should be stressed that most cases of breast cancer metastatic to the colon, as to other sites of the GIT, are of the lobular type: 15 of the 17 in the series of Taal et al. Two cases reported by Darcha et al. were also of the lobular type.
A particular form are mucosal polyps, either solitary or multiple, masquerading a polyposis.

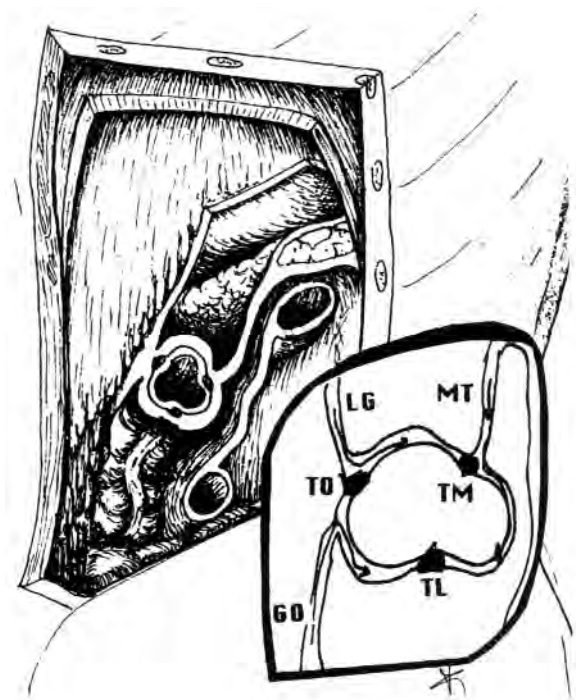

Fig.3.7 - The different pathways allowing spread of intra-abdominal tumors of the colon. (TO: taenia Omentalis; TL: teania libera; TM: tenia Mesocolica; GO: great omentum; LG: Ligamentum Gastrocolicum)

Symptoms

The presenting symptoms are not specific. In the few series published, diarrhea is prominent. Many cases were confused with Crohn's disease.

Diagnosis

Diarrhea in oncology patients can have many causes. The suspicion for metastases will lead to a colon enema or actually to a colonoscopy.

Imaging

The radiology of 30 cases with colonic metastases was reviewed by Wigh et al. They stress first the multiplicity of lesions (11/30), annular lesions (17/30), unilateral defects in 11/30 and marginal serration in 6. Several patients show large portions of the colon entrapped in a sheath described as encapsulation. This mainly has an influence on distensibility, and entails the possibility of collapse.

Table 3.23 - Metastases to the Colon
Differential radiological features (Meyers et al.)

Spread type	Most Common Primary Tumor	Growth Characteristics	Localization in Colon
Hematogenous	Breast cancer	Mucosal, submucosal or full wall thickness	none specific
Direct Invasion			Inferior border of sigmoid
1. contiguous structures	Ovarian cancer		
2. via mesenteric reflections	Stomach, Pancreas	Desmoplastic Desmoplastic	Transverse, superior border Transverse, inferior border
Intraperitoneal Seeding	Stomach, Pancreas Ovary, Colon	Desmoplastic	Sites related to ascites flow (1) anterior rectosigmoid (2) terminal ileum and cecum (3) superior border of sigmoid (4) lateral cecum-ascendens

Table 3.24- Metastases to the Colon from breast cancer
Radiologic features (N=17)
Series of Taal et al. (1992)

Stenosis	
Median length	19 cm (5-42)
Spasms	6 cases
Severity	
>1/2 lumen open	3
<1/2 lumen open	14
Contour	
Extrinsic compression	8
Irregular, interrupted	4
Apple core lesion	3
Mucosal destruction	3

Extrinsic pressure is common in benign tumors but the desmoplastic reaction results in fixation of the segment with or without kinking. Angulation of the intestinal wall and restricted motility is common (Krestin et al.). Fixation was seen in half of their cases. The mucosa looks usually normal, but in some somewhat stretched or thickened.
Reviewing 12 cases and features reported in the literature, Meyers et al. were able to distinguish a number of radiological features allowing to differentiate at a certain degree, the cause of metastatic colitis (table 3.23). The radiological features of colonic metastases have been studied by Taal et al., at least for breast cancer. In these patients, quite a long segment is subjected to stenosis, while in about half extrinsic compression adds to the pathology (table 3.24).

METASTASES to the RECTUM

Pathways

Several of the situations described as invasive are in fact from tumors of the neighbouring organs, mainly prostatic and urinary bladder.
For other tumors, hematogenous spread is obvious.

Incidence

No data, not even from autopsy series, are available. It is certainly a rare occurence as only case reports from extra-pelvic tumors have been published. One unexpected is that a number of breast cancers are involved primaries. There are also reports of a case of stomach and one small bronchus carcinoma.

In an autopsy series of 337 breast cancers, Ash et al. found 3 cases of which 1 was asymptomatic. A radiology series on symptomatic breast cancer patients found 7 rectal metastases of 17 colorectal metastases. Fifteen of them were of the lobular carcinoma type (Taal et al.).

Table 3.25 - Metastases to the Rectum
Literature review of the author

		Age
Breast Cancer		
Rees 1976	1 case of 4GIT(hist?)	55 yr
Chang 1978	1 case of 7GIT (hist?)	48
Balthazar 1979	1 case breast (9mo)	65
Lasson 1982	1 case scirrhous carc(11yrs)	69
Hoff1983	2 cases(Lob.-Aden.)	50 -55yr
Grosdidier1985	2 cases(Lob) 1type1 (°)	56 - 63
Haubrich 1985	1 case ductal (3yrs)	56
Koop 1988	1 case(') (Scirrh.)	71
Clavien1990	1 case of 4GIT(Lob)-syn	82
LeBouedec1993	1case of 8GIT(Lob)	60
Belumba..1993	1 case Type1(Lob)	61
Darcha 1993	1 case Type 1(Lob)	64
Stomach cancer		
Bayer 1993	1 case (poor different.)	M46
Balthazar 1979	2 cases	
Bronchus		
Johnson 1995	I case (small cell)	M50
Piriform Sinus		
Petit	1 case (epidermoid)(')	M45

(') rectosigmoid;
(°) mention of 2 other cases from previous literature

We collected 14 other cases, many 'buried' in small GIT metastatic series. Here too, there were 7 cases of

the lobular type, as is common for GIT metastases from breast cancers (Table 3.25). Three cases were type 1 or revealing metastases.

Pathology

In almost all symptomatic cases, the metastases presented as a stenosing infiltrating submucosal infiltration generally beginning at the serosa or extra-mucosal sites, and over a variable but relatively short length. On the contrary, primary colonic cancers develop in the mucosal epithelium.

Symptoms

Obstruction, bleeding and tenesmus are most frequently cited in the clinical presentation.
Tenesmus and 'false-need' were the first symptom of an unknown lobular breast cancer (type 1 metastases) reported by Belembaogo et al. and one by Darcha et al.

Diagnosis

A biopsy of the infiltrate disclosed the metastases in all reported cases. It is the mainstay of diagnosis.

METASTASES to the ANUS

This is a very rare situation. We are aware of only seven reports in the literature. The primaries concerned are one breast cancer, one bronchial and four colonic carcinomas. One of the latter was a revealing type presenting as a fistula, probably an ulcerated metastasis (table 3.26). The relative old age of the patients is a striking feature.
Some cases of colonic carcinoma metastatic to the anus have been reported. In cases of sigmoid carcinoma after an abdomino-perineal resection, it is difficult to differentiate it from an implant in the surgical suture.

Pathways

If hematogenous spread is obvious for extra-abdominal tumors, retrograd venous or lymphatic spread can explain anal metastases.

Table 3.26 - Metastases to the Anus
Literature data

Primary	Author	Patient	Symptom
Breast	Dawson 1985	F70(')	incr.constipation, discharge
Bronchus	Kawahara 1994	M75	prolapsed polyp
Colon	Killingbach 1965		
	Marchal 1970		
	Smiley 1988	M45	pain, bleeding
	Roullet 1990	M73	bleeding, pain
		F82	bleeding

(') lobular carcinoma

Symptoms

Summarizing the reports, rectal bleeding and discomfort were the main presenting signs.

Pathology

Differential diagnosis with a primary or recurrent rectal carcinoma is obvious, as a second cancer can occur.

Metastases to the PERITONEUM

Incidence

Although a common problem in daily oncology, at least for several tumors, credible or accurate data are scanty.

Table 3.27 - Malignant Ascites
Type of primary tumor
Relative incidence data from Garrison et al.

	N	1st complaint	
Abdominal N=54 or 50%(')			
Pancreas	20	14	18.6%
Liver-Biliary tract	4	3	
Stomach	8	5	7.4%
Colon	18	5	16.8%
Kidney	3	1	
Retroperiton.Sarcoma	1	0	
Pelvic N= 40 or 37.4%			
Ovary	18	15	16.8%
Uterus-Cervix	9	3	8.4%
Prostate	2	0	
Bladder	1	0	
Extra-Abdominal N= 23 or21.4%			
Bronchus	7	2	6.5%
Breast	3	0	
Testes	1	0	
Unknown	2	1	
Lymphoma	10	6	9.3%
TOTAL	107	56 (52%)	

(') Percentage of 107 patients with ascites

Peritoneal spread is common in ovarian, colonic and pancreatic tumors. Mucoid carcinomas and pseudomyxoma peritonei create particular problems.
The primary tumors of 107 consecutive patients presenting with ascites are listed on table 3.27. Half of them concerned abdominal tumors.

It is worth mentioning that of 56 breast cancer patients who developed clinical evidence of ascites, it was in 11 or 20% the first sign of metastases (Fentiman et al.). In another series of 65 patients with malignant ascites, the tumor was not found in 14 or 21.5%. In only two was the primary found at autopsy, both a pancreatic cancer (Ringenberger et al.).

Pathways

It has been shown that tumor cells follow the normal

flow of ascitic fluid, with implantation most likely occuring in particular areas of pooling

In order to better understand peritoneal spread and its related problems, a succinct description of the peritoneal cavities may be useful.

The abdominal cavity can be divided into two large compartments, the upper or supramesocolic and the lower or infra-mesocolic (Healy et al.). As the name states, they are separated by the mesocolon, extending from the back of the abdomen more or less horizontally towards the colon transversum. In both compartiments, a number of spaces are described (table 3.28) (Fig.3.8). The different anatomic structures are well described in the textbooks and will not be repeated here.

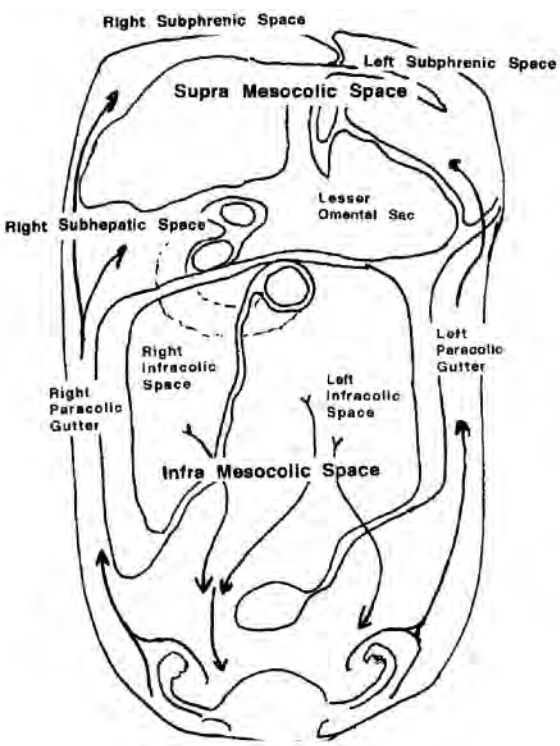

Fig.3.8 - The compartments and the spaces of the peritoneal cavity

Table 3.28 - The Peritoneal Compartments and Spaces Modified from Healy et al.

Supra Mesocolic Space	Infra Mesocolic Space
Ri. Supramesocolic S.	Ri.Infracolic Space
Ri. subphrenic Space	Le.Infracolic Space
Ri. Subhepatic Space	Ri.Paracolic Gutter
Lesser Sac	Le.Paracolic Gutter
Le. Supra Mesocolic S.	Pelvis
Le. ant. perihepatic S.	Douglas
Le. post. subphrenic S.	F. uterovesical Space
Post. subphrenic	recto-uterine Space
Le. ant. subphrenic S. (splenic) Space	M. rectovesical Space

All these compartements communicate freely with each other, so that fluid can move in either direction from one to another.

Peritoneal fluid moves in two ways

- by gravity from the upper parts downwards
- by negative intra-abdominal pressure from the pelvis towards the lateral gutters or resorbed towards the lymphatics at any site.

Certain locations are more frequently involved than others. The pouch of Douglas is invaded in about 50% of cases and is the most frequent location (table 3.29). The site of involvement is somewhat different for GIT-cancers and ovarian cancers. The latter invades the right paracolic gutter proportionally more, while the sigmoid mesocolon is much more frequently involved in GIT-cancers (fig.3.9).

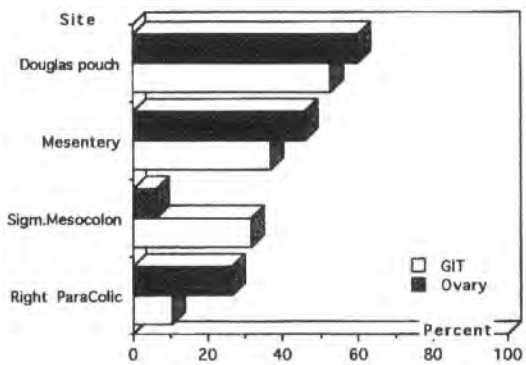

Fig.3.9 - Comparative frequency of involvement of the different peritoneal spaces between GIT and ovarian cancers (drawn from data of Meyers)

Table 3.29 - Peritoneal Metastases Involved areas (N=34) Data of Meyers

Douglas- Cul de sac	50%
Right lower quadrant (')	40%
Cephalad border of sigmoid colon	20%
Right paracolic gutter	20%

(') along root of small bowel mesentery

A further virtual cavity exists 'beneath' the parietal peritoneum, the subserosal space. The loose tissue between the abdominal wall and the parietal peritoneum forms a continuum with the loose space contained between the two blades of the mesenterial roots. It probably accounts for the spread of cells from the pelvic or retroperitoneal organs up to the intestinal mesenterial blades.

The subserous space, an anatomic plane persisting from embryonic stages to adulthood, is the basis of the thoraco-abdominal continuum. There is enough clinical material illustrating the fact that different diseases can spread directly from the abdomen to the subpleural space (fig.3.10). The subpleural space can be defined as the area adjacent to the visceral pleura. The continuum is that portion of the subserous space traversing the diaphragmatic hiatuses connecting

subperitoneal and subpleural portions of the subserous space (Oliphant et al.).

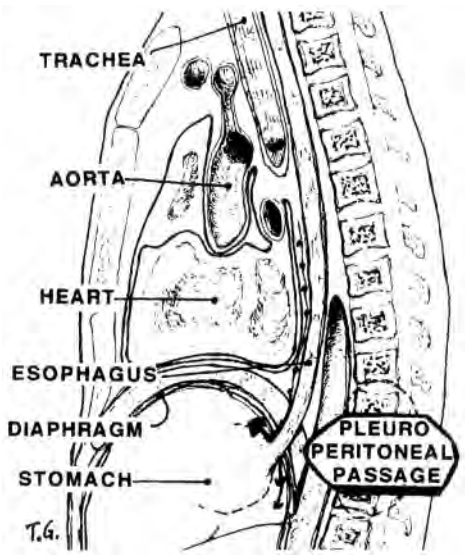

Fig. 3.10 - Sagittal section of the thoraco-abdominal continuum or pleuro-pulmonal passage, allowing migration from the pleural to the peritoneal cavities

Pathology

Spratt and Sugarbaker have shown that three types of peritoneal metastases can be distinguished.

1 .Hematogeneous spread from extra-abdominal tumors such as breast, thyroid and bronchus. They are in fact metastases of the small bowel and mesenterium.

Tumor emboli will be carried through the mesenteric arteries, penetrating the mesenteric border of the small bowel and arborizing the vasa recta. These smaller vessels course to the anti-mesenteric border, the convex margin facing away from the mesenteric root, where the cells will implant and grow with characteristic nodules. Melanoma and breast emboli grow within the submucosa along the anti-mesenteric border, often producing intramural nodules. They can extend to the lumen and develop central ulceration.

Metastases from bronchogenic carcinoma can produce large masses along the mesenteric borders, tethering mucosal folds and fixing them in angulate bowel loops (Levitt et al.).

2. Implantation on the peritoneal surface or intra-abdominal cancer spread or a direct invasion through the gastrointestinal wall (penetration through the intestinal wall) or ovarian capsule (penetration through the capsule). This can occur with low-grade tumors, but is much more frequent in high-grade cancers.

3. Chylous ascites.

When the cancer has invaded and disrupted retroperitoneal lymph nodes and channels, fluid can accumulate intra-abdominally. It is caused by interruption of flow at any point from the intestinal villi to the mesenteric and abdominal lymphatics, the main lymphatic duct and the left brachiocephalic vein. The invasion obstructs the lymph flow upward to the ductus thoracicus. Tumor thrombus within diaphragmatic channels can be another cause.

Press et al. collected 26 consecutive cases presenting over 20 years. There were 7 non-oncologic causes, 13 caused by a lymphoma and 8 by solid tumors (table 3.30).

4.Omental Cake

Bulky and infiltrative masses within the great omentum by contiguous spread and growth of tumors from the stomach, colonic, pancreatic and most frequently ovarian cancers. This most often results from widespread intraperitoneal seeding. It has been described for extra-abdominal tumors, but this is not frequent (Rubesin et al.).

Table 3. 30 - Chylous Ascites
Cause of presentation (N=26)
Data of Press et al. 1982

Non-Oncology: trauma, congenital etc.	7
Lymphoma and Myeloproliferative	13
Solid Tumors	8
Pancreas 2, Breast 2, Colon, ovary, kidney, Prostate each 1	

At the microscopic level, malignant cells can migrate, within the cavity or along the peritoneum in several ways (fig 3.11):

1. Seeding of cells from the fluid into the serosal surfaces;
2. Spread along the surface;
3. Spread between the blades of the mesenterium, possibly also from the subserosal (pelvic or retroperitoneal) spaces (Oliphant et al.);
4. Full-thickness invasion from any tumor from any organ within the cavity through the serosa (visceral peritoneum), with further seeding (transserosal);
5. The leakage of tumor cells from transect lymphatic channels, as is common per- and postoperatively;
6. The hematogenous spread occurs as tumor emboli within the mesenterium;
7. When tumor cells and tumor emboli spread in the peritoneal cavity, implantation on the serosa ensues.

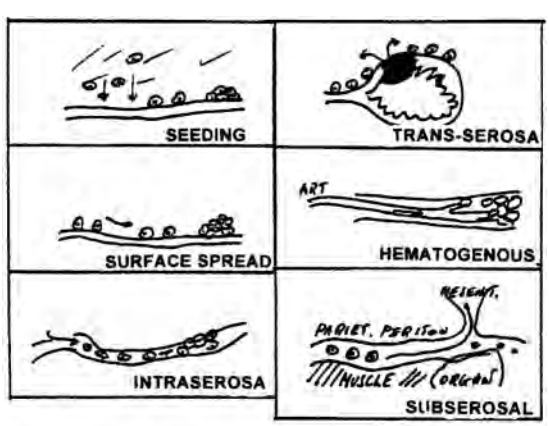

Fig.3.11 - The different types of spread of malignant cells in and over the peritoneum.

Although cellular dissemination usually has a low efficiency, this process however has a high efficiency, due to the specific biology of the peritoneal surface.
The spread of large amounts of fluid collection within the peritoneal cavity is influenced by the histopathology of the tumor and its grade. As they can freely move from any space to another, they can be arrested by a number of structures or follow anatomical folds and blades.
Moderate and high-grade tumors result in early implantation of the cells on the surface of the serosa, even even where there is a high volume of ascites. Sugarbaker called this the randomly proximaly distribution.
Low-grade cells do not adhere easily to the surface near the primary. The presence of mucin causes a complete redistribution through the peritoneal cavity, resulting finally in widespread dissemination with high quantities of mucus, and interfering with cell adhesion.
At the macroscopic level, several patterns can be observed: certain tumors spread along neighbouring peritoneal structures. Fluid collection follows the anatomic folds and recesses within the peritoneal cavity (fig.3.13).

- Stomach cancers spread down the gastrocolic ligament to the superior border of the colon;
- Cancer of the transverse colon can spread up this ligament towards the stomach;
- Carcinoma of the pancreas extends directly along the transverse mesocolon involving the postero-inferior border of the transverse colon.
- Cancers of the hepatic flexure can spread along the transverse mesocolon towards the paraduodenal areas (Levitt et al.).
- Tumors of the pelvis will first invade the Douglas and then either follow the lateral gutters or spread within the left intra-colic space.
- Tumors with widespread involvement can form large and bulky tumors within any peritoneal blade, especially the great omentum (omental cake).

We would like to point out that there is one 'open' port towards the cavity, namely the ovarian tube. This is also a much-discussed cause of spread from endometrial, but also of tubal carcinomas. The ovary lies normally beneath the peritoneal serosal surface, but a tumor can invade through the serosa and seed within the abdominal cavity.

Based on their large clinical and surgical experience, Deraco et al. have summarized the characteristic distribution of most pelvi-abdominal tumors when they come to an intra-peritoneal spread. The primary and its location will determine the type of anatomical spread and the resulting appearance at surgery, radiology and even at autopsy can be deduced (table 3.31).

It has been stated that hematogenous metastasis presents a different radiographical appearance and depends on the site where the metastasis starts from an intra-abdominal cancer. Melanoma and extra-abdominal tumors result in more peritoneal implants ranging from single to multiple ones. They can evolve to ulcerating masses invading the small bowel.

Fig.3.12 - Possible pathways of tumoral spread along ligament and other structures within the peritoneal cavity.

Table 3.31 - Peritoneal Spread type and Histology Modified from Deraco et a l.

	Randomly Proximally Distribution	Complete Redistri- ution	Widespread Cancer Dissemination
PseudoMyxoma P.		+	
Appendix carcinoma			
Cystadenocarc. G1		+	
Cystadenocarc. G2-3			+
Adenocarcinoma	+		
Carcinoid	+		
Colorectal cancer			
Mucinous G1.2.3			+
Intestinal	+		
Gastric cancer			
Diffuse	+		
Intestinal	+		
Ovarian carcinoma			
Serous	+		
Mucinous			+
Diffuse Mesothelioma		+	

Any lesion of the peritoneum must be considered malignant. Clinical pattern, age, an history of previous oncology treatment and the radiological appearance may help to discern the source or kind of peritoneal process.

Table 3.32 - Role of the Peritoneal Ligaments in the Dissemination of Neoplastic Processes
From the text of Meyers et al. 1987

Ligament	Spread mode
Coronary	From Ri.anterior pararenal space to bare area of the liver
Gastrohepatic	Invasion by nodes from stomach, distal esophagus, pancreas, breast, bronchus From upper part of stomach (fundus) to left liver lobe From gallbladder to pancreaticoduodenal system and lymph nodes
Falciforme	Cullen's sign, from liver to umbilicus
GastroColic	Spread of gastric tumors down to superior haustra of transverse colon
Transverse mesocolon	Continuity between pancreas to lower border of transverse colon, up to splenic flexure, spleen, small bowel from Ri. colic flexure to descending duodenum from colon lymph nodes towards the central superior mesenteric nodes
Duodeno-Colic	Same as transverse Mesocolon
Gastrosplenic and Splenorenal	Spread of gastric malignancies to the spleen and to tail of pancreas
Mesentery	From the small bowel towards lymph nodes Spread of pancreatic tumors to the small intestine
Phrenico-Colic	Spread of pancreatic tail tumors to the anatomic flexure of the colon.

The peritoneal ligaments (fig.3.13), as the several folds at the posterior side of the abdomen can be called, also play an important role in the 'guided' dissemination of tumorous processes (Meyers et al.). A tabulated overview is given on table 3.32 and figure 3.12.

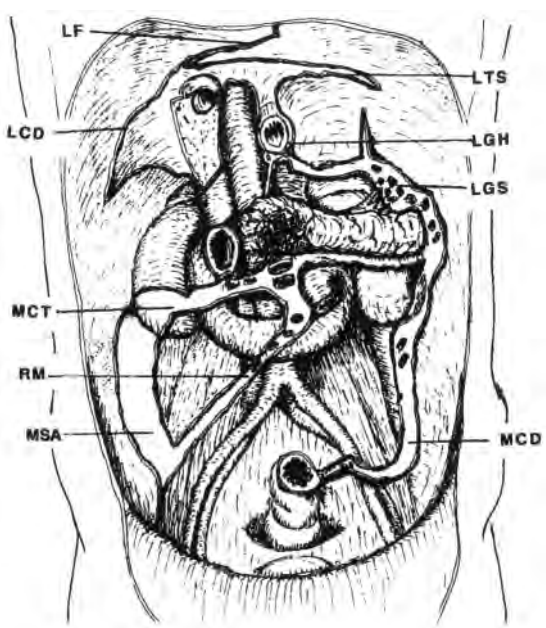

Fig.3.13 - The posterior wall of the abdomen, showing a number of virtual spaces outlined by peritoneal reflections and giving structure to a number of ligaments and roots. LF: ligamentum falciforme; LCD: lig.Coronoria Dextra; MCT: Mesocolon Transversum; RM: Radix Mesenterii; MSA: Mesocolon Ascendens; MCD: Mesocolon Descendens; LGS: Lig.Gastrosplenicum; LGH: Lig. Gastrohepaticum; LTS: Ligamentum Triangulare Sinistrum

The delineation of at least attempts or even trials for aggressive treatments of peritoneal carcinomatosis has led to new insights into this dreadful and previously considered fatal clinical situation.

A staging method has been proposed as a landmark for treatment evaluation by Gilly et al. and was recently applied in a multicenter French study (table 3.33).

Table 3. 33 - Peritoneal Carcinomatosis
Staging Proposal (Gilly et al.,Sadeghi et al.)

Stage 0	No macroscopic disease
Stage I	Malignant granulations with dimensions less than 5mm. Localized in one part of the abdomen
Stage II	Malignant granulations with dimensions less than 5mm. Diffuse within the whole abdomen
Stage III	Malignant granulations 5mm to 2cm
Stage IV	Large malignant cakes (more than 2 cm)

This study collected 370 patients with a non-gynecological malignancy in the period 1995-1997 and reported many interesting demographic and anatomic data. In more than two-thirds it concerned digestive cancers (table 3.34) (Sadeghi et al.).

Table 3. 34 - Peritoneal Carcinomatosis
Non-Gynecologic Malignancies
Demographic Data, taken from Sadeghi et al.

Site	N	% male	mean age	At 1st(')
Stomach	125	60.8%	60.5	58.5%
Pancreas	58	46.6	65.5	69.0
Colo-rectal	118	52.5	62.3	58.4
Unknown	43	34.8	67.5	---

(') Peritoneal carcinomatosis present at first diagnosis of the tumor

The peritoneal carcinomatosis was staged HI-IV in about 60% of all patients.

Interval

As can be expected, the occurence of peritoneal effusion is much earlier in cases of ovarian carcinoma than breast. Data were provided by Vande Molengraft et al. (table 3.35).

Table 3. 35 - Peritoneal Effusion -Ascites
Time interval according to primary
Data of VandeMolengraft et al.

Primary	Average
Breast cancer	136.8 weeks
Ovaries	48.4
Lymphoma	53.8

Type 1 Presentation

A large series on cytology of malignant peritoneal effusion was reported on by Sears et al. Of the 311 patients with a positive cytology, the primary was unknown at presentation in 53 or 17.0%. No epidermoid cancer presented with a malignant effusion initially. After investigation, the primary remained unknown in 14 patients or 29% (table 3.36).

Table 3. 36 - Malignant Peritoneal Effusion
Primary Unknown at presentation
Data of Sears et al.1987

Adenocarcinoma (N=47)	
Ovary	24 or 51% of the adenocarcinomas
Pancreas	2
Stomach	3
Tuba Fallopii	1
Liver cancer	1
Appendix	1
Not Found	14 or 29% of adenocarcinomas
Non-Epithelial	6 (4 lymphomas)

Symptoms

Symptoms are obviously either caused by the volume of fluid accumulated, with mechanical compression on the intra-abdominal organs. Other symptoms are caused by the primary tumor.

Table 3.37 - Patients with Chylous Ascites
Symptoms and Clinical Finding (N=28)
Series of Press et al. 1982

Symptoms		Physical finding	
Abd. distension	25	Ascites	25
Abdominal pain	16	Pleural effusion	17
Anorexia	14	Low. extrem. edema	15
Weight loss	13	Enlarg.lymph nodes	11
Edema	12	Caput medusae	10
Weakness	10	Cachexia	9
Nausea	9	Abdomoinal mass	8
Dyspnea	8	Hernia	5
Weight gain	5	Cysto-Rectocoele	4
Lymph nodes	4	Tender abdomen	3
Early satiety	3		
Fever - sweats	2		

Clinical symptoms possibly associated with peritoneal metastases and/or ascites are pain, discomfort, and cramps due to subobstruction and loop fixation. Increase of girth, abdominal fullness and increasing discomfort are signs of increasing abdominal volume.
In advanced stages, intestinal obstruction and perforation with fistula and/or abcess formation and peritonitis occurs. Ascites may occur and chylous ascites can result from invasion and disruption of retroperitoneal lymphatics.
Press et al. have reported findings specifically relating to chylous ascites in a group on 28 patients (table 3.37).

Imaging

Before the CT era, imaging of peritoneal or intra-abdominal tumoral spread was almost impossible, except in very advanced cases, when the encasement and invasion of intestinal structure could be visualized to some extent.
Sonography can demonstrate superficial peritoneal and omental tumor nodules. When ascites is minimal ultrasonography is relatively unable to detect nodules.
The possibilities of US in the diagnosis of malignant ascites and peritoneal dissemination were studied by Goerg et al. While 60, or 92%, of their patients showed at least one abnormality, these were usually only present as so-calledindirect signs. Direct signs such as visualization of peritoneal metastases was only obtained in 16 or 25%. Indirect signs such as multiseptate ascites, echoes within a fluid space, omental matting and adhesion of bowel loops, were only each present in 25%.

CT has indeed revolutionized the diagnostic possibilities, even at early stages.
It is the only imaging method able to provide useful quantitative information on peritoneal carcinomatosis. The distribution of tumor implants in the different abdomino-pelvic regions can be assessed and can delineate the different metastases.
Large foci of metastatic carcinoma frequently have eccentrically located areas of decreased density within them, probably due to central necrosis. Small masses down to 1cm are detectable and are readily recognizable.
In order to enhance the sensitivity of CT, intra-peritoneal infusion of contrast material was introduced. A comparative study of CT with and without has been made in 35 patients, but could not demonstrate any clear superiority (Nelson et al.). They obtained interesting data. The sensitivity to disease detection in the greater omentum and the small bowel mesentery was relatively low, compared with the fact that at laparotomy the involvement was very high in these sites.

In table 3.38, the site involvement in the abdomen as confirmed at laparotomy is indicated, and to a certain extent somewhat corroborates the value obtained in a smaller group by Myers. (see also fig.3.11).
CT is an important method of screening the abdomen. Its sensitivity is best when there is a significant attenuation difference between tumor and adjacent non-tumorous parenchyma.

Table 3.38 - Peritoneal Carcinomatosis
Intra-abdominal site involvement
Data from Nelson et al. (')

	At Laparo	CT sensitivity IP+	IP-
Right subphrenic space	60-84%	56%	88%
Left subphrenic space	40-60%	75	83
Porta hepatis	60-85%	59	67
Splenic hilum	53-54%	100	86
Right paracolic gutter	53-73%	60	73
Left paracolic gutter	60-63%	75	67
Greater Omentum	84-86%	50	50
Small bowel mesentery	85-87%	59	38
Pelvis	80-84%	69	75
Abdominal wall invasion	25-60%	20	44
Retroperitoneal invasion	10-27%	0	100

(') results in two groups of patients at surgery.
IP+: sensitivity of CT with IP; IP- without.

However, one particular challenge is the detection of peritoneal metastases. Tumor deposits tend to occur at sites coinciding with the natural flow of peritoneal fluid (fig.3.10): the superior aspect of the terminal ileum, the medial aspect of the cecum, the posterior aspect of the sigmoid colon, the pelvis, the paracolic gutter and the subhepatic and subphrenic spaces on the right (Nelson et al., table 3.38). A CT with rapid I.V. administration of contrast allows diagnosis of peritoneal abnormalities by enhancement of peritoneal lining.
CT certainly provides a more complete evaluation of the whole abdomen than sonography can. The adjunct of pneumoperitoneum has reduced the threshhold of detectability of peritoneal implants, and obtained a better visualization of intraperitoneal adhesions. However, it is time-consuming and does not evaluate all the peritoneal recesses potentially involved (Caseiro-Alves et al.).
MRI does not seem to afford better definition than CT for peritoneal implants. The lack of adequate GI. contrast agents and motion artefacts are the causes. Nevertheless, MRI can show the various manifestations of peritoneal seedings (Chou et al.).

Ascitic fluid is often loculated, sometimes septated and maybe present or absent in the different compartiments. Both US and CT can detect small amounts of ascites (Thoeni). In appropriate conditions, sonography can detect easily at least 100 ml, but much less when the location is anterior to the liver or immediately below the diaphragm. CT can detect smaller amounts, and with helical techniques it is considerably faster.
The presence of loculation, a rounded or oval collection is a helpful feature to recognize malignancy. They exert a mass effect on adjacent bowel or intra-abdominal organs, sometimes even in an intra-abdominal organ. It can be observed in about half of the patients (Walkey et al.).
Chylous ascites at CT has the typical attenuation-density of water, but sometimes the fluid will separate into oil-water level, or even an incomplete mixing pattern (Hibbeln et al.).

The diffuse neoplastic infiltration of the greater omentum (omental cake) has a distinctive CT-appearance. A soft tissue mass is seen separating the colon or the small intestine from the anterior abdominal wall, with obliteration of the normal fat plane in the area. CT will show masses within the pelvis above or below the peritoneal blade. These masses are typically well circumscribed and have walls of variable thickness (Levitt et al.).

Four distinct patterns of omental involvement have been distinguished by Cooper et al.

1. replacement of the normal fat by large solid masses of 'caking';
2. small nodules and a finely infiltrated fat-smudged appearance;
3. cystic masses with lower attenuation centers, and
4. multiple discrete nodules.

The first two types were most frequently observed and in all different primaries, either abdominal or extra-abdominal. The latter types were rare. The pattern is however not specific for a malignant process, as it has also been observed in tuberculous peritonitis.
The authors noted that tumors involving the omentum by direct extension (as in liver cancer), showed more focal CT abnormalities. More generalized abnormalities are observed in malignancies spreading diffusely over the peritoneum.

Walkey et al. have stated that involvement varies with stage. Early disease is marked as irregular soft-tissue densities within fat, like an omental permeation or marbled fat. In later stages, discrete nodules with heterogenous contrast enhancement will be observed. In more advanced stages, the classic omental cake is observed. Another pattern in the advanced stage is a spread in a contiguous fashion involving stomach and/or transverse colon.

When the small bowel is adequately opacified with oral contrast, mesenteric masses can be much better demonstrated and distinguished.

The presence of ascitic fluid can help show up parietal implants, as small excrescences, particularly lateral to the liver, where small bowel loops do not hamper identification. Parietal peritoneal thickening and enhancement occurs in several cancers, with a predilection for the right diaphragm, the cul-de-sac and right paracolic gutter. It can present as a thin, sometimes nodular, enhancing line along the surface. It is a useful sign of malignancy, except that it can also occur in tuberculous peritonitis (Walkey et al.). They have summarized the CT-findings in 73 patients with peritoneal metastases (table 3.39).

Calcifications of the metastatic noduli over the peritoneum is rarely seen. Some cases have been reported which could even take up radioactive bone

tracers (Teplick et al.). Magnetic Resonance Imaging offers superior soft tissue contrast to CT, but has no serious diagnostic advantages over CT.

Table 3.39 - Peritoneal Metastases
CT-features observed in 74 patients
Data of Walkey et al.

Ascites	74%	Omental cake	12%
Loculation of Ascites	34	Bulky perit. tumor	5
Greater sac only	42	Pseudomyx. perit.	3
Greater and lesser sac	32	Calcifications	1
Parietal thickening	62	Bowel distortion	49
Parietal nodules	42	Omental nodules	26
Permeated omental fat	30	Obstruction	11
Thickening of bowel wall	42	Adenopathy	25
Liver metastases	15		

Peritoneal Metastases in Children

This has received only scant attention in the literature. It was identified in 32 patients, in 20 at the initial diagnosis, but the number of the total population was not given (Kaste et al.).

Table 3. 40 - Peritoneal Metastases in Children
Data of Kaste et el. 1998

Colon Carcinoma	5 cases
Rhabdomyosarcoma	4
Germ cell tumors	6
Wilm's tumor	3
Melanoma	2
Lymphoma	2
Various	10

It occurred in the 12 patients between 2 months and 6.2 years after diagnosis of the primary, median 1.1 years. A number also had other concurrent metastases. The peritoneal metastases were seen at CT at a mass lesion in 26, peritoneal enhancement in 15, peritoneal studding by small implants in 11 and diffuse caking in 4. More than one type of metastases was present in 15, or half of the patients.
The primaries involved are on table 3.43.

Diagnosis

While clinical examination can assess the presence of ascites and even of localized abdominal infiltration, it remains very crude and can only raise suspicion.
Cytology is sensitive and worthwhile, but does not accurately reflect the overall tumor bulk.
Several authors have emphasized that the distinction between a transudate and exsudate is obsolete. The serum-ascites albumin gradient is much more appropriate to classify ascites.
Another parameter is the serum albumin value minus ascites fluid albumin.
The normal peritoneal fluid protein concentration is more than 40g/liter (Bac et al.). The albumin gradient correlates only with one physiological factor, namely the portal pressure. Consequently, a wide gradient, or more than 11g/L. can be described as portal hypertensive.
The wide gradient will be observed in any liver disease or involvement, while the narrow gradient is observed in peritoneal carcinomatosis, but also peritoneal inflammation.

Fibronectin, a glycoprotein with values above cut-off level of 50 or 75 mg/mL in ascitic fluid has a diagnostic accuracy of 95 resp. 100% in differentiating malignant from non-malignant ascites. Cholesterol also seems of value in the differentiation, malignancy being present when above 48 mg/dL.
Triglycerides are only useful for chylous ascites. The values are above serum level in chylous leakage.

PseudoMyxoma Peritonei

A gelatinous intraperitoneal fluid collection associated with mucinous tumor implants on the peritoneal surfaces and omentum is the characteristic presentation of pseudomyxoma peritonei (PM). Aside of a few non-oncologic origins, the condition is usually associated with malignant tumors, especially ovarian (40%) and appendiceal (29%) (table 3.41). The third most common primary is however the colon (Sugarbaker et al.; Zoetmulder et al.).

Table 3. 41 - Pseudomyxoma Peritonei
Repartition of Primaries in large series reported

Author	N	Ovary	Ov+Ap.	App.	Colon	Other
Wertheim 1994	23	16	3	4	--	--
Costa 1994	35	8	--	11	9	7(')
Hsieh 1995	9	3	--	3	1	2
Total	67	27	3	18	10	9

(') stomach 4, small bowel 1, bladder 1, unknown 1

Table 3.42 - Pseudomyxoma Peritonei
Unusual Primaries as case-reports

Author	Patient	Primary	Interval
Mendeloff 1971	M49	Urachus	simult.(A°)
Chejfec 1986	M57	Pancreas	simult (A)
MacCarthy 1988	F60	Tuba	simult
Friedman 1990	F49	Tuba (fimbria)	simult.
Hawes 1991	F72	Breast	simult(')
Kurita 1994	??	Bronchus adenoca	???
Ikejiri 1996	M76	Stomach	simult
Bloget 1996	F37	Teratoma omentum	simult
DeBree 2000	M34	Urachus	2yrs

(') patient had also serous cystadenocarcinoma of the ovary, but histology of peritoneum mass was from breast

Reviewing the literature, DeBree et al. found reports on several other primaries, as from cancer of the breast, the bronchus and the gallbladder (table 3.42).
The initial clinical presentation is usually abdominal distention sometimes with chronic progressive pain or a palpable mass. On physical examination the distended abdomen is evident, in the absence of hepato- or

Table 3.43 - Overall Abdominal Spread of different Tumors
Modified from text of Deraco et al.

APPENDIX Carcinoma

Adenocarcinoma and Carcinoid:
lymphatic and vascular spread, later distant
(similar to colorectal cancers)
Mucinous type : 100% peritoneal spread
Grade I : alike pseudomyxoma peritonei
Grade II-III: complete redistribution OR
randomly proximal distribution
In 30 % allready peritoneal spread at initial staging

COLON Carcinoma

Common: Lymphatic and hematogeneic spread
Peritoneal spread: cells present in 10% initially
Intestinal type:
mainly randomly proximal distribution
better survival than mucinous type
Mucinous type: peritoneal spread in larger volume

Carcinoma of the STOMACH

Recurrence in Peritoneum : 50%
Associated with serosal infiltration and
malignant cells within the cavity
High incidence of proximal distribution
Associated random distribution by gravity,
towards right paracolic gutter and pelvis.
- Correlates with histology type:
diffuse type : 45-70%
intestinal type : 10-30%
- Ovarian dissemination for both 30-35%

Carcinoma of the OVARY

Remains intraperitoneally for a long time.
Usually: contiguous spread,
invasion of abdominal and pelvic surfaces
invasion of peritoneal surface
of neighboring structures as from
bladder, sigmoid, tube
spread along right paracolic gutter
spread along omentum and liver capsule.

Mechanism :
flow of abdominal fluid due to negative intra-abdominal pressure, as a result of respiration.

Mesothelioma PERITONEI

Rare
frequently associated with ascites
Stages : locally, limited or diffuse, last most common.
Dissemination is different from pseudomyxoma P.

The major accumulation happens on peritoneal peritoneum, with early localization in the great omentum.

Progression:
massive accumulation at
right diaphragm
pelvis
later parietal peritoneal surface
liver, spleen; small bowel surface.

splenomegaly. The shifting dullness is commonly absent (Hsieh et al.).
Cystic or septal masses, diffuse abdominal masses and ascites are revealed at CT. The ascites is usually heterogeneous and of fat density with attenuation values higher than water. Septations and loculi can frequently be seen. Sometimes curvilinear calcifications. It seems that MRI may prove more helpful than CT in assessing the rare visceral invasion by the mucinous tumors (Walensky et al.).

Extraabdominal dissemination is very rare. A few cases have been reported extending towards the pleural, even pericardial cavity or mediastinum, most probably through the diaphragmatic ports (Mortman et al.).
The diagnosis is almost never correct at first presentation, but recently adequate imaging should make suspicion more frequent.

Metastases to the MESENTERIUM

The mesentery is a broad fan-shaped fold of the peritoneum connecting the loops of jejunum and ileum to the posterior abdominal wall. It consists of two layers of peritoneum, enclosing small bowel,arteries and veins, nerve plexuses, lymph vessels lymph nodes and connective tissue with a variable amount of fat.

Pathways

The metastases in the mesenterium are either hermatogenous through the mesenteric arteries or as has been described above, through spread of tumor cells along the mesenterial blade or peritoneal surface.

Imaging

Metastases in the mesenterium are clinically indistinguishable from any peritoneal involvement. In most cases they are simultaneously involved, but tumors (adenocarcinoma and carcinoids) of the small intestine can spread within the mesenterial lymph nodes.

CT obtains excellent definition of mesenteric diseases. Reviewing 370 scans, Whitley et al. found 95 positive cases, of which 47 lymphomas, a common source of

abdominal involvement. They define four patterns of mesenterial involvement: rounded masses, cake-like masses, ill-defined masses and a stellate mesentery. In lymphomas, mainly rounded and ill-defined masses were observed. Stellate masses were frequent in non-lymphomatous diseases, while all types were observed in ovarian carcinoma.
As discussed previously, the imaging problems and interpretation are alike those discussed for peritoneal metastasis.

Mesenteric tumor seeding is more difficult to delineate. The most common manifestation is a disarray of the bowel-mesentery pattern, suggesting peritoneal spread even when discrete masses cannot be localized within the ascites (Walkey et al.).
There have been reports of a few cases were a distinct metastatic spread was observed, at first described as mesenteric panniculitis.
Described as an infiltration of lipid-laden macrophages, the condition has been reported to rarely occur with metastases. There can be a single or multiloculated fatty mass with fibrotic capsule lining, with cystic areas, radiating bands and calcification. It will compress or displace the mesenteric vessels without invading them.
It originates in an obstruction of the lymph vessels in the involved mesentery.

Clinically, a non-tender, solid and mobile mass can be palpated in the mesogastrium.
It has been reported in ovarian and uterine cancers. The final diagnosis is histology.

Overall Lesson

An important lesson to be taken from this chapter is that the possibility of an intra-abdominal, intestinal or intra-cavitary metastasis can present in patients with a previous or known malignancy at any site, when they develop complaints or changes in the bowel habitus. Such patients can even present at emergency. Any primary from breast, bronchus to prostate can develop metastases at this site.
Otherwise, patients may present with GI-symptoms or complaints either from primary cancers in the abdominopelvic cavity or from other extra-abdominal cancers as first presentation.

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Caution: References are given for documentary purposes. Not all have been reviewed or used in the redaction of the text. We do not claim completeness of data. The references are as much as possible grouped per subject heading.

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4

METASTASES to the UROGENITAL SYSTEM

Metastases have been reported in all anatomical parts of the urogenital system. The most frequently involved sites are the kidney and the ovaries, though a large number of reports have dealt on metastases to the penis. Overt symptomatology and clinical awareness are the keys to diagnosis.

METASTASES to the URINARY SYSTEM

Metastases in the urinary system are not uncommon. They have been described in all parts of the system, but they are the most frequent within the kidney.

METASTASES to the KIDNEY

Pathways

It has been stated that the metastastic rate in the kidney is much lower than one whould expect in view of its significant vascular supply. The kidney receives about 20% of the cardiac output.
Entrapment of the metastatic cells is presumed to occur within the renal glomeruli or proximal arterioles and result in a diffuse pattern within the kidney. The vascularity of the glomeruli in the cortex is ideal for the entrapment of tumor emboli.

Pathology

The majority of the metastatic growths are found in the cortex as nodules and are arranged in a segmental vascular way with a wedge-shaped or rounded appearance. The cortical preponderance is probably due to the high number of glomeruli within this part (Thomas et al.).
Pathology studies by Wagle et al. revealed a capsular and stromal spread pattern in more than 90% of their 81 patients. Glomerular metastases were however found in only 6.2%.
Intraglomerular metastasis are rarely detected, in spite of the fact that this site is the first reached by the migrating cells. Only a few reports of autopsy cases are at hand.

As reported by Sridevi et al., two patterns of intraglomerular metastases can be distinguished: a 'diffuse intra-capillary' in which the tumor cells grow diffusely in all the glomerular tufts, and a diffuse 'extracapillary' where the parietal epithelium of the Bowman's space is replaced by tumor cells.

At autopsy, the lesions are usually multiple and bilateral in about 60% of the patients with renal metastases. Renal metastases are almost always part of widespread disease, at least at autopsy. In all cases reported by Mitnick et al. there were bilateral lesions, with a mean size of 3.8 cm (range 1 to 11 cm).
In 61% of the 816 patients taken from a series of 11328 patients, Bracken et al. measured the size of the renal metastases (table 4.1).

Table 4.1 - Metastases to the Kidney
Size and Site of the Metastases
Data of Bracken et al. 1979

Size		Site	
<1cm	29.0%	Cortex	25%
1-3cm	21.6%	Medulla	4%
>3cm	10.6%	Both	31%

A rare presentation of diffuse small metastases in the pyelocaliceal system was reported in a patient with rectal cancer. It occurred 16 years after surgery in a M74 (Rioux-Leclercq et al.).

Incidence

Incidence rates at autopsy vary between 3 to 15% of

cancer patients (table 4.2).
The most frequent primaries are, in descending order, tumors of the bronchi, the breast, the stomach, pancreas, colon, kidneys and esophagus (table 4.3). More than 30% of the renal metastases are from melanomas, but overall, they form only 5% of the metastases from that primary. This illustrates the relatively low frequency of renal metastases.
Examining the records of 81 patients with secondary renal tumors, Wagle et al. found the following data:

- no gender difference
- bilateral metastases in 50%
- no predilection for any anatomic pole
- metastases were diffuse in only 9/81.

Table 4.2 - Metastases to the Kidney
Literature data

Author Year	N	Data
Klinger 1951	5,000	renal M in118, >80% bilateral
Wagle 1975	4,413	renal M in 81 : 20% bronchus, 12% breast

Lagrange 1988 found 103 literature case reports diagnosis in vivo : 53% bronchus, 11% melanoma, 10% GIT.
Becker 1978-1981 1,131 renal M 40 or 3%

Table 4.3 - Metastases to the Kidney
Primary Tumor involved (*) - data of Wagle 1975

Bronchus	19.8%(**)	Ovary	2.5%
Breast	12.3	Bone	2.5
Stomach	11.1	Tongue	2.5
Kidney	8.6	Ileum	2.5
Esophagus	4.9	Bladder	2.5
Pancreas	3.7	Thyroid	2.5
Biliary tract	3.7	Adrenal	2.5
Testes	3.7	Mouth	2.5
Colon	3.7	Bone	2.5
Cervix Uteri	2.5		

(*) only those with more than one patient are listed
(**) percentage of the series

The series of Wagle contained only epithelial tumors, melanoma being absent in the data. A more comple-te data set was published by Bracken et al., based on autopsies of 11328 oncology-patients (table 4.4), in whom 816 had renal metastases.
Of 281 oncology patients, 16 (5.7%) were found to have renal metastases. CT had not detected 11 of these (Nishitani et al.).
Melanoma patients have the highest incidence of renal metastases, while testis also has a high rate. Gynecological tumors have the lowest rate.
Altough renal metastases are said to be mainly part of widespread process, Choyke found solitary renal metastases in 3/27 (11%) patients. In the large series of Bracken et al., a solitary metastasis occurred in 21.5%. On the other hand, one series (Benoit et al.) mentions 12 cases of renal metastases, of which 5 were the first presentation of a cancer of the pancreas, the ovary, the bronchus, a sarcoma and a melanoma.

Table 4. 4 - Metastases to the Kidney
Primaries at Autopsy (N=816)
Data of Bracken et al. 1979

Primary	N	Nwith M	% of N
Bronchus	1255	224	17.8%
Melanoma	417	148	35.5
Breast	968	80	8.3
GenitoUrinary			
Testis	127	29	22.8%
Kidney	150	20	13.3
Adrenal Gland	50	14	28.0
Prostate	256	11	4.3
Penis	17	2	11.8
Gastro Intestinal			
Esophagus	150	15	10.0%
Stomach	225	13	5.8
Pancreas	154	25	16.2
Colon	166	23	13.9
Gynecology			
Cervix Uteri	492	24	4.9%
Uterus	137	4	2.9
Ovary	316	12	3.8

Intraglomerular metastases are rare. In a series of 136 oncology patients, Sridevi et al. detected only 42 with renal metastases and in 4 only (or less than 3%) of these glomerular metastases were detected. Two concerned a bronchial cancer, one the pancreas and one from a pulmonary teratoma.

Clinical Pattern

Although rather common in oncology patients, renal metastases are rarely clinically evident and usually found only at autopsy. Modern imaging methods and systematic investigations are now able to detect many during the patients' life time.
When symptomatic, hematuria and/or flank pain are the most frequent complaints. Hematuria is caused by bleeding of metastatic lesions, while flank - ureter pain can be caused by blood clots or even tumorous tissue.
There have been reports of patients where hematuria was profuse and life-threathening such as in choriocarcinomas and other hypervascular tumors. It was the first symptom of a widespread parenchymal renal metasta-ses of a pancreatic cancer diagnosed at autopsy (Loughran et al.).
In the series of Wagle et al., all patients had albuminuria and 31% had microscopic hematuria. No other symptoms were listed, but none was asymptomatic. A literature survey is presented on table 4.5.

Table 4.5 - Metastases to the Kidney
Symptomatology in 69 literature cases
Survey by Lagrange et al. 1988

Hematuria (sole or concomitant)	39
Flank pain	31
Palpable mass	5
Proteinuria	4
Fever / asthenia	4
No symptoms	5

The time-interval between diagnosis of the primary and the renal metastases was shorter than 1 year in 41/69 or 60%. The mean interval was 1.5 year (Lagrange et al.).
In the series of Choyke et al., the mean interval time was 2.2 yrs, with 30% discovered within one year. One noteworthy aspect was the long interval in breast cancer patients: 5 and 6 yrs in their two patients.

Imaging

Plain film and excretory urography is now completely obsolete in the detection of renal metastases. The method detects only large lesions and in an indirect way by distortion of the excretionary system or contour abnormality.
Ultrasonography is the first method that should be applied. It is very sensitive, but can miss smaller lesions, lesions with similar echotexture or in obese patients. The sonographic appearance is of a homogenous hypo-echoic mass, but heterogenous or echogenie metastases have been reported.

Computer tomography is better for visualizing the number and the extent of the metastases, as it also detects smaller ones. At CT, the lesions are typically multifocal, contained within the renal margin and either isodense or slightly low in attenuation (10-40 H.U.). The small lesions typically do not enhance or only faintly on contrast administration (5-15 HU) (Bailey et al.). This is confirmed by Mitnick et al.
One noteworthy aspect is that on enhanced CT, the tissue attenuation of the metastases is very close to normal tissue, making the metastases difficult to discern from the kidney. Contrast-enhanced CT shows metastases as areas of low attenuation compared with the enhanced kidney parenchyma (Mitnick et al.).
Differential diagnosis with cysts can be difficult. Metastases have however irregular and thickened walls and the soft tissue enhances more. Low echogenicity allows differential diagnosis with cysts (Volpé et al.).
The possibility of a second primary renal cancer must be taken in account, as stressed by Pagani. At CT, these tumors are much large, single and with disrupted kidney contours. The caliceal system is displaced, obstructed or invaded compared with metastases which are mostly multiple and with interference on the caliceal system.

Based on a study of 45 patients, Ferrozzi et al. distinguished seven different patterns:
1. Multiple hypodense lesions, generally small and bilateral. They have a peripheral location and lack of contrast enhancement.
2. Single voluminous lesions with fluid content.
3. Diffusely infiltrating hypodense lesions, massively involving the kidney. This results from a diffuse metastatic embolization process and a subsequent global involvement.
4. Hemorrhagic lesions with mild contrast enhancement. This occurs in typical hypervascular malignancies as choriocarcinomas, melanomas, leiomyosarcomas and malignant 'apudomas'.
5. Lesions with foci or calcification. Malignancies with a propensity for calcification such as osteo- and chondrosarcomas. Such lesions indicate a highly probable malignancy. Secondary calcification due to dystrophic changes and/or necrosis of tumor tissue can occur in some mucoid or papillary carcinomas.
6. Lesions involving the perirenal space. Either the lesion bulges out of the kidney as in many bronchial carcinomas, or it results in an irregular contoured mass with thin streaks infiltrating the space. This is seen often in malignant melanomas.
7. Hypovascular homogenous single solid lesions.

The authors could not correlate the pattern with any typical primary except for in the 'exceptions' discussed above.

No single imaging appearance is diagnostic for renal metastases. Nevertheless, some primaries have some distinctive characteristics (Volpé et al.). The metastases of squamous bronchial carcinoma regularly present with a necrotic center or with a diffuse infiltrative pattern. Choyle found small multifocal parenchymal nodules from bronchial cancers. Colon carcinoma usually presents with large exophytic masses, which can be confused with primary renal carcinoma. Metastases from melanomas are rather small and multifocal and more likely to infiltrate the perirenal space.

Angiography has been advocated but this seems to be useful only in selected cases. Metastases are typically hypovascular and contain no neovessels. There is no arteriovenous shunting nor a significant blush, except in some hypervascular tumors such as choriocarcinoma and melanoma. It has been suggested that renal metastases retain the vascular pattern of the primary, but this is not the rule.
An indication of angiography is the preparation when therapeutic embolization is considered.

There has been incidental diagnosis with radioisotope scintigraphy of renal metastases from osteosarcoma and with iodine scintigraphy of thyroid carcinoma

Diagnosis

Imaging with ultrasonography is the first 'screening' step in symptomatic patients, to be followed if necessary with CT.
Needle biopsy can be useful, but urinary cytology is simple, inexpensive and very rewarding in malignant melanoma and squamous cell carcinomas.
As the incidence of a new primary renal cancer is much more frequent than renal metastases, differential diagnosis is necessary. The imaging difference has been discussed above. At abdominal CT in 1000 oncology patients, Pagani found seven patients with an abnormal kidney. In six of them, a second renal

cancer was confirmed at biopsy and in only one the metastases from a colonic carcinoma. However, all these patients did have other metastases.

METASTASES to the PERINEPHRITIC SPACE

This anatomic region lies between the renal capsule and the anterior and posterior leaves of Gerota's fascia. It contains a rich network of vessels and lymphatics. It is a site of metastatic dissemination, probably mostly lymphogenous. Melanoma is probably the most frequently metastasizing tumor at this site.
Onuigboo's assertion that bronchial tumors reach this zone by retrograde lymphatic spread is probably true. Anyhow the most frequent pathology in this region consists of metastatic processes (Wilbur et al.). This is common in thymoma (see chapter 8).

Three pathways have been suggested:
1. via the para-aortic nodes of the abdomen;
2. via the pleural and diaphragmatic lymphatics;
3. via connecting trunks from intrathoracic juxta-vertebral and intercostal nodes.

The symptomatology is dominated by flank pain. CT is the imaging method of choice. It shows a more or less enhanced soft tissue mass, with abutted perirenal fat.

METASTASES to the URETER

Pathways

Extension from retroperitoneal lymph nodes is frequently described as ureteral metastasis. Strictly speaking, this is not correct and it should be considered as contiguous invasion. Hematogenous spread should be less common and was described for a malignant melanoma (Babaian et al.). Recent reports describe ureteral metastases more correctly (table 4.6).

Table 4.6 - Metastasis to the Ureter
Pathways described

1. Involvement via the renal pelvis and ureter
2. Involvement by direct extension from neighbouring organ: direct invasion, compression or encasement
3. Hematogenous spread within the ureteric wall

Pathology

The following types have been described:
1. all or portion of the layers of the ureter with evidence of tumor cells in the muscular layer, perilymphatic or vascular components;
2. periureteral adventitial metastases with compression of the ureteral wall;
3. local mucosal metastases with or without involvement of the muscularis layer;
4. secondary to extensive retroperitoneal involvement.

Criteria for definite diagnosis of true metastasis have been proposed by Presman et al.:
1. a malignancy involving the ureter with a growth within the wall;
2. tumor present in the periureteral lymphatics;
3. no involvement of the ureter by direct extension or contiguity.

Single or multiple lesions can occur. In the series (37 cases) of Babaian et al., 31% were in the proximal, 46% in the mid and 23% in the distal segment.The left side was involved in 49%, the right in 26% but 25% bilaterally. According to Alexander et al., there are several reports of contralateral ureteral metastases from a clear cell carcinoma of the kidney.

The renal parenchyma was entirely replaced by multiple tumor masses of between 1 and 7cm in a patient (M68) who had been treated for sepsis 4 years after resection of a rectal cancer. The diagnosis of renal metastases was not suspected before autopsy (Issa et al.).

Incidence

Its incidence is low. In 1979, Babaian et al. could find fewer than 150 reported cases (table 4.7).
In 11,698 necropsies (1944-1975), 37 or 0.3% ureter metastases were histologically proven.

Table 4.7 - Metastases to the Ureter
Incidence data from Literature

Autopsy		
Kirshbaum 1933	4,860	5 cases
Abrams 1950	1,000	4.3%
Lucke 1957	365	62 (17%) cases
Cohen 1974	3,200	31 cases
Klinger 1975	5,000	7cases
MacLean 1956	10,233	18 cases (7 outside urinary tract)
In vivo:		
Grabstald 1969	24 cases of breast cancer	

Table 4.8 - Metastasis to the Ureter
Literature review by Fitch et al. 1976

Breast	44	Kidney	4
Stomach	22	Pancreas	3
Bladder	17	Uterus	2
Colon	12	Ureter	2
Cervix Uteri	12	Urethra	1
Rectum	11	Esophagus	1
Prostate	11	Thyroid	1
Ovary	5	Pleural	1
Melanoma	5	Skin basal cell	1
Lung-Bronchus	4	Thymus	1

The primary tumors causing this type of metastasis are very different. A literature review done in 1976 is given in table 4.8. and one from 1986 (table 4.9). The preponderance of breast and cervical cancer is remar-

kable. This explains why ureteral metastases are twice as frequent in females as in males.
The interval from diagnosis of the primary to the diagnosis of the metastases is noteworthy: the median interval was 12 months. Of the cases of Babaian et al., 74% were discovered only at necropsy. We have no data on the amount of solitary or multiple locations in the patients.

Table 4.9 - Metastasis to the Ureter (N=460)
Literature review by Akmal et al. 1986

Cervix Uteri	161	35%	Urin.Bladder	16	3%
Breast	96	21%	Uterus	12	2.5%
Colorectal	46	10%	Pancreas	9	2%
Stomach	31	7%	Ovary	4	1%
Prostate	29	6%	Gallbladder	2	0.5%
Bronchus	18	4%			

Clinical Pattern

Metastatic ureteral tumors generally occlude the ureteral lumen. This can be caused by
1. growth and encroachment with invasion of a tumor nodule;
2. a sclerosing reaction to the tumor resulting in the formation of the stricture;
3. edema through invasion, and
4. invagination (intussusception) of the upper ureteral segment into the lower one (Alexander et al.).

Symptomatology

When symptomatic, the metastases will cause ureteral colic and eventually subsequent progressive hydronephrosis. In more than half of the patients however, they are asymptomatic and found only at autopsy (Cohen et al.).

Table 4.10 - Metastases to the Ureter
Symptomatology
Literature review by Akmal et al. 1986

Symptom	
Dysuria / Mictur. probl.	32% (*)
Flank pain	32%
Hematuria	31%
Anuria	29%
Fever - chills	23%
Oliguria	15%
Back pain	15%
Laboratory Finding	
Elevated uremia	71%
Urin.tract infection	63%
Pyuria	35%

(*) not every symptom was noted in the reports

Ureteral obstruction with pain in the flank or colic, sepsis and interference with renal function are the presenting symptoms. Hydro-uretero-nephrosis will thus be a common finding on pyelography. As mucosal involvement with or without erosion is not common, hematuria is not a frequent presenting symptom.

Modern imaging methods allow detection of these metastases at a much earlier phase.
A literature review by Akmal et al. has show as could be expected that the symptomatology is not specific, and more or less relates to the (sub)-obstruction of the ureter (table 4.10).

Imaging

Obstruction of the ureter at any level can sometimes be observed accompanied by hydroureter and/or hydronephrosis. Irregularity in the contour of the ureter was another sign.
CT has now supplanted plain urography for the diagnosis of ureteral metastases.
When a bone scan shows a hydronephrotic aspect of the kidney, ureteral obstruction must be suspected.

Diagnosis

The diagnosis will rely on the clinical and imaging findings. Urinary cytology can be of academic value.

METASTASES
to the URINARY BLADDER

Pathways

Secondary bladder tumors have been classified according to their origin in three ways:
1. Those reaching the bladder by contiguous extension and invasion from a cancer of the adjacent organs such as prostate, rectum, cervix uteri or sigmoid colon. As we have already stated for other tumors, these are not true metastases and will not be considered further here. They are stage IV tumors.
2. Others reach the bladder by implantation of exfoliated tumor cells from transitional epithelial or papillary carcinomas. This is no longer accepted and the bladder tumor must be considered as a multi-centric field carcinogenesis.
3. True metastatic tumors originate from cells arriving there via the hematogenous route, either by arterial, venous or lymphatic means.

Table 4.11 - Metastases to the Urinary Bladder
Literature Survey (two series)

Primary	Ganem 1956	Goldstein 1967
Stomach	25/80	34/146
Melanoma	18	55
Breast	16	16
Bronchus	6	11
Rectosigmoid	3	3
Testis	2	2
Pancreas	2	4
Kidney	2	14
Ovary	2	2
Cervix Ut.	1	1
Uterus	1	1
Cecum Colon	1	2
Gallbladder	1	1

Incidence

Metastases to the bladder comprise a small but significant percentage of stomach tumors. A literature survey conducted in 1956 disclosed 80 reported cases (Ganem et al.) (table 4.11). The main tumors appeared to be stomach, malignant melanoma and female breast cancers. A new survey ten years later obtained the same proportions (Goldstein).

In 1974, Melicow reported on a series of 114 secondary vesical tumors, and gave separate data for both genders (table 4.12). The data between parentheses are most probably cases of contiguous invasion.

Table 4.12 - Metastases to the Urinary Bladder
Data of Melicow N=114 (1974)

Site	Men (N=56	Women(N=58)
Bronchus	3	1
Stomach	8	6
Colon	3	6
Rectum	(10)	--
Prostate	(23)	--
Kidney	1	--
Breast	--	12
Ovary	--	9
Uterus-Cervix	--	(17)

A review of 5,200 necropsies in male patients disclosed 21 patients with metastasis in the bladder: 8 melanomas, 6 from a stomach cancer, 5 bronchial and 1 of pancreas and one of the colon. Data according to the number of patients coming to autopsy (table 4.13), have allowed the calculation of the metastatic intensity of the different primaries.

Table 4.13 - Metastases to the Urinary Bladder
Incidence according to primary
Autopsy data of Sheehan et al. ,1963

	N	meta	percent
Malignant Melanoma	37	8	22%
Stomach cancer	125	6	5%
Bronchial tumors	688	5	0.8%
Pancreas	96	1	1%

The kidney is mentioned as another frequent source of bladder metastases. There were 19 documented cases in the literature between 1909 and 1986. By 1993, these had increased to 31.

Perez-Mesa reported bladder metastases in 3.3% of 341 patients with mammary carcinoma coming to autopsy. Only in 4 of the 11 patients were the metastases found during life. Nevertheless, the tumor had infiltrated the muscularis in most of them.

When bladder metastases are present they are usually part of a widespread process. At autopsy retroperitoneal and periaortic nodes together with extrinsic and intrinsic ureteral metastases are commonly involved.

Bladder metastases in breast cancer patients are observed late in the evolution, usually several years after treatment of the primary. The interval ranged from 7 months to 7 years, except in one patient, where the diagnosis was made simultaneously with that of widespread metastases (literature review by Silverstein et al.). In the three recent reports, a long interval was also observed.

Pathology

Metastatic lesions often infiltrate the wall of the bladder rather than ulcerating the mucosa. The result is that malignant cells do not appear in the urine. Another consequence is that many metastases are asymptomatic. Several cases have been reported where the bladder metastasis is solitary (Bardales et al.).

Symptomatology

Metastases in the bladder can be asymptomatic or overshadowed by the symptoms of widespread metastases. When symptomatic, they do not differ from a primary bladder carcinoma. As metastases are not frequent, the differential diagnosis with a new primary must be considered.

Symptoms will occur when the mucosa is involved. Most of the metastases will only be found at autopsy. Dysuria, hematuria, pollakisuria are as can be expected most frequent. This will prompt a cystoscopy and biopsy.

Imaging

Irregular filling defectsn either single or numerous, throughout the bladder can be observed, but in several examined cases, no abnormality was noted. Double contrast exams have been proposed, though CT has now supplanted plain RX for the detection of metastases.

Diagnosis

Cystoscopy with biopsy is the mainstay of diagnosis. Cytology of the urine is a non-invasive method, but its accuracy can be questioned. As stated above, many metastatic lesions do not shed cells in the urine, because of their intra-mucosal location.

One important caveat that a substantial percentage of prostate carcinomas may shed cancer cells into the urinary bladder without involvement of the bladder wall. In many cases, metastatic cells are indistinguishable from primary signet ring cell primary bladder carcinoma. (Bardales et al.).

METASTASES to the MALE GENITAL SYSTEM

We will discuss in turn metastases in the testis, epididymis, the prostata, the penis, the sper-matic cord and the seminal vesicles. In general, the metastatic incidence in these organs is low.

METASTASES to the TESTIS

Pathways

The arterial route is the most probable one for extra-abdominal tumors metastasizing in the testis.
Abdominal tumors, or tumors which involve abdominal organs may spread via the retrograde venous pathway. The involvement of retroperitoneal, para-aortic and iliacal nodes may well explain any spread along a retrograde lymphatic route (table 4.14).
The vas deferens, epididymis and rete testis is one suggested and possible route to explain testicular metastases from prostatic carcinoma.

Table 4.14 - Metastases to the Testis
Pathways (Kirkali et al.)

1. arterial embolism (hematogenous)
2. retrograde venous extension
3. retrograde lympatic spread
4. direct extension
5. intraluminal through vas deferens.

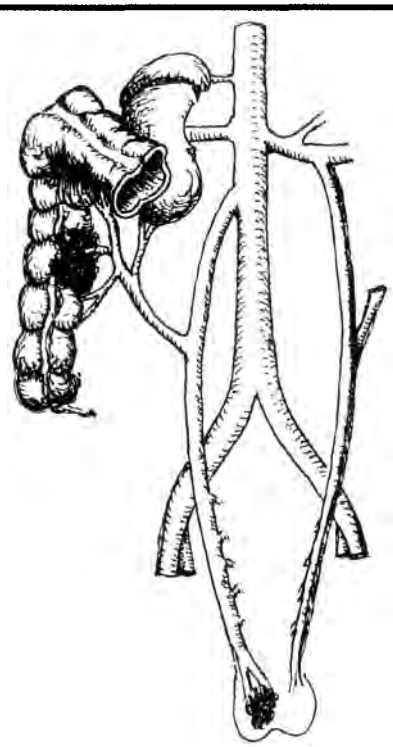

Fig.4.1 - The venous drainage of the testis explaining the reflux-metastases from a colonic cancer

The testicular vein leaves the internal inguinal ring, ascends upwards as a single trunk and divides midway between the origin and lower pole of kidney into two branches, a medial and a lateral. The lateral division follows the lateral border of the kidney, ending in the perinephritic fat. All along its course are several venules communicating with the colonic veins. These anastomosis are found in 76 % of the individuals examined.
The medial branch ascends upwards terminating on the left in the renal vein, but at right in the inferior vena cava (Washiha). In half of the individuals, several communicating veins are found crossing the midline between both ascending veins.
This may explain the occurrence of metastases from the kidney, colon and pancreas within the testis.

Incidence

Reviewing 24,000 autopsies, Pienkos et al. found 15 cases or an incidence of 0.06% They found 90 cases in the literature (table 4.15). Of 1,600 testicular tumors sent to pathology, Price et al. encountered 38 secondaries or 2.3%. In an autopsy series of 335 male patients with malignancies, 7 had testicular involvement, or 0.02%. However, 25% of these patients had a malignant hematology disease, skewing the results somewhat. Testicular involvement is indeed frequent in lymphomas.
A literature review in 1992 was able to document about 200 cases since 1935.

Table 4.15 - Metastases to the Testis
Literature review Pienkos(1972)

Prostate	39 cases	Retinoblastoma	2
Bronchus	14	Carcinoid ileum	1
Kidney	9	Bile ducts	1
Colon	9	Appendix	1
Stomach	6	Adrenal	1
		Unknown	1

The most recent report on testicular metastases included 20 patients (Patel et al.). Of 550 testicular tumors, there were metastases in 3.6%, half of them bilateral and the left localization being in the minority.
In pathology series one must rely on the histology examination of orchidectomy material in patients with prostatic carcinoma, although this is rarely stated. Of 80 patients submitted to orchidectomy, Johansson et al. found metastases in 5 or 6%. The case reported by Addonizio et al. was also detected on a orchidectomy-specimen. Other authors have figures between 3 to 5% (Kirkali et al.).

Table 4.16 - Metastases to the Testis
Literature review Haupt (1984) N=129
(.) the number of revealing metastases

Prostate	45(2) cases	Retinoblastoma	2(0)
Bronchus	25(0)	Urin.Bladder	2(0)
Melanoma	12(0)	Carcinoid	2(1)
Colon	11(1)	Bile duct	1(0)
Kidney	10(2)	Ureter	1(0)
Stomach	6(1)	Salivary Gland	1(0)
Pancreas	5(1)	Thyroid	1(0)
Neuroblastoma	3(0)	Unknown(')	2(1)

(') poorly diff. adenocarcinoma

Interesting data were provided by Haupt et al, who

reviewied the literature in 1984. Of the 129 reported cases, 9 or 7% were the first sign of a subsequently found primary (type 1-metastases). Simultaneous bilateral metastases were found in 19 or 15%. Each side was involved at the same rate (table 4.16).
The most frequent primaries are prostatic cancer, bronchial carcinoma or malignant melanomas. Four years later, the number of reported cases was 218 or almost double in number. The already cited primaries still accounts for the greatest number, but cases from adrenal, rectum, penis, appendix, bile ducts and salivary glands have been added (Meacham et al.).
It is striking that the incidence of testicular metastases, at least in bronchial cancer, is much lower than adrenal metastases. The 'soil' characteristics are probably the reason, but the lower temperature of the testis might be another reason, as well as the some what 'remote' testicular vasculature.

Pathology

Testicular metastases can present as a focal nodule or a diffuse involvement. The tumor often occupies the interstitium with relative sparing of the seminiferous tubules, which are then compressed and become atrophic and hyalinized (Haupt et al.).
Three types of growth patterns or involvement have been described (Lurie et al.):

1. infiltration of interstitial tissue, surrounding normal seminiferous tubules;
2. diffuse involvement of testicular tissue with destruction of the tubules;
3. rarely, spread of tumor cells within the seminiferous tubules with minimal invasion of the interstitium.

Differential diagnosis with primary tumors is obvious. Metastases usually present in older patients, while primaries usually present in the second or third decade.

Symptoms

The case reports in the literature show that most tumors are found by the patient as a slow growing painless mass. Nevertheless, the alert clinician also finds them during clinical examination, though this is rarely mentioned.
A small nodule may well escape the attention of the patient and the clinician, and then only be found at autopsy, or in therapeutic orchidectomy specimens.

Imaging

Echography has been done in some cases, showing an intratesticular proces.

Diagnosis

The presence of a testicular swelling in a young patient, where there is a known extra-testicular tumor should rise the suspicion of one other primary tumor. A testis tumor in older patients is, however, more likely to be a metastatic proces.
Fine needle cytology is certainly adequate and easy to perform. Cytology or histology of the orchidectomy will give the final diagnosis. In cases of widespread metastases, this can be discussed. A biopsy is more appropriate for learning about the nature of the tumor. The presence of testicular metastases is usually part of a widespread process, in bone, lungs and/or abdomen.

METASTASES to the EPIDIDYMIS

Pathways

The epididymis is a rare recipient of metastases. An hematogenous route is very probable, but a retrograde route along the vas deferens from the prostate and even the bladder might be a plausible alternative (table 4.17).

Table 4. 17 - Metastases to the Epididymis Pathways

1. Hematogenous route as arterial embolism
2. Retrograde lymphatic extension
3. Contiguous invasion from neighbouring organ
4. Retrograde venous extension or embolism
5. Retrograde spermiduct extension

Lymphatic vessel occlusion through a pelvic tumor or from the retroperitoneal nodes is a likely explanation for the urogenital cancers metastatic to the epidydimis. Arterial embolism metastases are commonly accompanied by other distant metastases.

Incidence

Up to 1981, only 9 cases had been reported in the literature. Three of these were detected in orchidectomy specimens. Ganem et al. state that up to 1998, less than 40 cases of metastases to the epididymis had been reported.

Table 4.18 - Metastasis to the Epididymis Literature survey / number of reports

Prostate	26	Stomach	8
Colon	14	Pancreas	2
Kidney	12	Liver	1
Bladder	2		

The majority are from a prostate primary. Case reports on metastatic tumors from several other primaries have appeared (table 4.18).
A type 1 metastasis from a sigmoid carcinoma was reported by Smalman, one from a cecal tumor (Ramesh), one from a pancreatic carcinoma by Faysal and another one from a stomachal cancer (Olesen et al.).

Symptoms

In the few cases reported, a localized painless swelling was the revealing sign. While a ultrasonography could be of interest, this has not been reported until now. Diagnosis will be final with resection.

METASTASES to the PROSTATE

Pathways

Metastatic cells can reach the prostate by arterial circulation. Retrograde venous and lymphatic flow is, however, probably more frequent.
Contiguous invasion is frequent from neighbouring cancers such as bladder and rectosigmoid cancers, and are not to be considered true metastases.

Incidence

Metastases in the prostate have rarely been reported. It is probable that they are usually hidden within a widespread pelvic metastatic proces.
A large, and to our knowledge, the only documented series was published in 1985 by Zein et al. In autopsies of 5,962 male subjects, there were 469 primary and 328 secondary prostatic tumors. Metastatic involvement is apparently as frequent as primaries, but in 143 it clearly involved an invasion from neighbouring cancers.
Furthermore, leukemic or Hodgkin or non-Hodgkin-lymphoma was present in 127 cases, leaving 57 or 2.36% of the cancer patients with a definite prostatic metastasis. The concerned primaries are on table 4.19.

Table 4.19 - Metastases to the Prostate
Primary Tumors (N=57)
Autopsy data from Zein et al. 1985

Primary Tumor	N	with M	Percent
Malignant Melanoma	204	12	5.9% (°)
Pancreas	156	4	2.5
Bronchus	1,233	31	2.5
Germ cell tumor	128	3(')	2.3
Thyroid	63	1	1.5
Stomach	250	3	1.2
Kidney	225	2	0.9
Esophagus	151	1	0.7

(') two in testis and one extragonadal
(°) percent of the patients with this primary

The most frequent primary seems to be the bronchial cancer, but proportionally they mainly derive from malignant melanoma.
In the period to 1981, Cihak et al. found 57 patients in the literature presenting with symptoms of prostatic obstruction.

Symptoms

Prostatic involvement will probably present with urinary obstruction. The age of many cancer patients will probably lead first to a diagnosis of prostatic hypertrophy, unless a biopsy or TUR reveals the metastatic involvement.
The patient reported by Cihak et al. was a type 1 metastases revealing an asymptomatic and unknown renal cell carcinoma.

METASTASES to the PENIS

Pathways

A rich vascularity makes frequent metastases within this organ likely. Compared with the other organs of the male urogenital system, the reports on metastatic involvement are relatively numerous. We found about 137 references.
Anatomical accessibility is probably the main reason for the frequent diagnosis.
A hematogenous route is the most probable for supradiaphragmatic tumors, but retrograde venous and lymphatic flow can disseminate malignant cells from abdominal or pelvic tumors, including renal neoplasms, to within the corpora cavernosa (Abeshouse et al.).

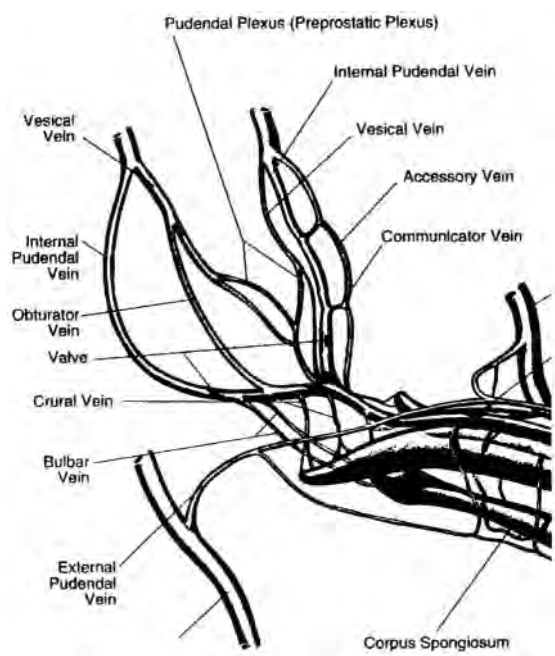

Fig. 4. 2 - Venous anatomy of the Penis

There is a marked difference in the venous drainage of the left and the right kidney. The left (ovarian or spermatic) vein always joins the left renal vein, whereas its termination occurs in the right only in 20%. The left renal vein is frequently the center of an intricate venous network in communication with the adrenal, visceral, diaphragmatic and lumbar venous channels. On the right side, the venous components end in the inferior vena cava rather than the renal vein. There is also a widespread communication between

a) the deep dorsal venous system and the venous supply to the bladder and the prostate, and
b) the pelvic venous sytem and the visceral lumbar, spermatic and lower limb venous components after any injection of the dorsal vein of the penis (Abeshouse).

The bulbs and the crus both drain via several veins to the internal pudendal vein (fig.4.2). The glans drains into the deep dorsal vein, with direct communication between the glans and the corpora cavernosa. The deep dorsal vein drains to the preprostatic plexus and the internal pudendal vein. The superficial dorsal penile vein drains to the external pudendal vein and then into the saphenous.

When a proximal tumoral obstruction is present, the venous blood current will reverse permanently or temporarily according to the variation in the intra-abdominal or intra-thoracic venous blood pressure.
Tumor emboli may extend into the left spermatic vein and pampiniform plexus of the spermatic cord and involve all the low pelvic and genital organs by virtue of the communication with the pelvic venous system.

A retrograd lymphatic way is presumed to occur only in cases of low pelvic lymphatic involvement. The lymphatics of the perineum, the anus and the lower rectum drain to the inguinal nodes following the inferior hemor-rhoidal and internal pudendal vein. As these vessels supply the penis, the corporal bodies of the prostate and the ischiocavernous muscles, a lymphatic extension from the prostate, bladder and rectum may proceed along this road (Abeshouse et al.).

Pathology

Almost all the metastases are located in the corpora cavernosa, either within or at the periphery, bulging into the skin. Metastases in the urethra, without involvement of the corpora is very rare (Iverson et al.).

Incidence

A review was published by Perez et al. in 1992. They found about 300 cases in the literature (table 4.20). About one quarter are from non-genito-urinary tumors. According to a review by Chan et al., 460 cases had been reported by july 1997. As with many metastases, they may have been underreported even for autopsy cases.
The primaries most frequently involved are of the genito-urinary sphere such as prostate carcinomas (about 30%), and the urinary bladder (about 30%). Adding about 10% of the cases originating from kidney carcinomas, almost 70% are of the urinary tract. A retrograde venous or lymphatic flow is a sufficient explanation for this. Of the non-genito-urinary tumors concerned, more than half were in the rectocolon.

Table 4.20 - Metastases to the Penis
Review by Perez et al. 1992

Genito-Urinary Primaries (N= 229) 75%			
Urinary Bladder	97 cases	Renal pelvis	2
Prostate	93	Ureter	2
Kidney	25	Spermatic cord	1
Testis	9		
Non- Genito-Urinary Primaries (N= 75) 25%			
Esophagus	1	Bronchus	10
Stomach	1	Nasopharynx	3
Colon	5	Supraglottis	1
Rectum-Sigmoid	45	Heart	1
Anus	2	Bone	3
Liver	1	Pancreas	1

Symptoms

The external location of the penis is probably a reason why metastases are found more readily there than in the other neighbouring organs.
It has been claimed, that 30% of the metastases are asymptomatic.
Urinary difficulties, palpable or visible nodules and priapism are the most frequent symptoms and reasons to seek medical advice (table 4.21).

Table 4.21 - Metastases to the Penis
Initial presentation (N=88) (Chan et al.)

Nodule	51%
Priapism	27
Any urinary symptom	27
Pain	17
Urine retention	13
Skin lesion (edema or ulcer)	11

There is no specific symptom for a metastatic process in the penis. The infiltrating aspect must be differentiated from the induratio penis plastica or Peyronié's disease.
Almost all patients have multiple other metastases.

Imaging

Although imaging studies are, in fact, not appropriate further to the diagnosis, ultrasonography could be useful in order to differentiate with other lesions, as far as benign swellings of the penis must be excluded.
One case was extensively studied with different modalities (Andresen et al.). Ultrasonography showed a hypo- to iso-reflexive structure, possibly infiltrating the tunica albuginea. Duplex sonography revealed perifocal hyperemia without visualization of the deep penile artery distal to the tumor. The tumor was visible at CT but its extent and invasion could not be delineated. Even a MRI confirmed the occlusion of the penile artery and the absence of infiltration to the tunica. Cavernosography has also been proposed, but we doubt the utility of the procedure (Escribano et al.).

Diagnosis

The first diagnosis relies on palpation and knowledge of the presence of a primary tumor elsewhere. FNA cytology or wedge biopsy will confirm the pathology, to the extent that this is necessary in case of widespread metastases.
'Revealing' cases (type 1 metastases), from renal and rectal carcinoma are particularly noteworthy.

METASTASES to the SPERMATIC CORD

Pathways

The spermatic cord is a very rare site for metastases. The pathways will be similar to those for the epididymis or testicle.

Incidence

Reviewing the literature Issa et al. could only find 29 cases up to 1994. (table 4.22), to which they added one case originating in the urinary bladder.
The high frequency of gastric cancer is striking. Many reports are from Japan where stomachal cancer is endemic. One case with metastases type 1 or revealing the stomach tumor has been reported.

Table 4.22 - Metastases to the Spermatic Cord Literature review by Issa et al.1994

Stomach	19 (65%)	Kidney	1
Pancreas	2	Prostate	1
Colon	2	Appendix	1
Rectum	1	Ureter	1
Bladder	2		

METASTASES to the SEMINAL VESICLES

Metastases in the seminal vesicle (SV) are a well-known prognostic factor for prostatic carcinoma.

Pathways

Törnblom et al. suggest two theoretical routes. Malignant cells may be vehiculated by the semen, though semen normally does not enter the seminal vesicles. Hematogenous or lymphatic spread along the deferential vein of the testis is probably the cause.

Incidence

Autopsy studies have shown that invasion of the SV by prostatic cancer is relatively frequent (table 4.23).

Table 4.23 - Incidence of Invasion of Seminal Vesicles

		N	N with invasion
DeLaMonte	1986	89	57(64%)
Lamothe	1986	I69	58(34.3%)

The data's acuracy will however depend on the diligence of the pathologist, or on the number of surgically treated patients. We found no data in the literature that could prove otherwise.

Pathology

Pathology studies by Graham et al. found a metastatic rate of 50-60% in prostatic cancer patients. Their studies indicate that micro-vascular invasion of the SV is predictive of tumor progression. Freely anastomosing microvascular channels may represent a significant pathway for the dissemination of prostatic carcinoma.

One case of metastasis within the SV has been reported in a patient operated 2 years before for a testicular non-seminomatous carcinoma (Törnblom et al.).

METASTASES to the FEMALE GENITAL SYSTEM

We will now in turn look at the metastatic processes in the ovaries, the uterus, the vagina and the vulva. The literature on uterine metastases is somewhat fuzzy as endometrial, myometrial and cervical metastases are not always clearly separated from each other.
Data comparing the incidence of metastases in the different female pelvic organs have been provided by Mazur et al. Including genital primary cancers there were 113 metastases in the ovary, 7 in the endometrium, 5 in the cervix, 20 in the vagina and 3 in the vulva. This confirms that the ovaries are relatively the most frequent site of metastases. A small number (13) had two metastatic sites.
In general terms, compared with the male genital systems, metastases in the female genital system are relatively much more frequent. The hormonal influence is a possible explanation, although many occur in the postmenopausal period.
In this chapter we include also metastases in the placenta and those in the uterine leiomyoma.

METASTASES to the OVARY

Pathways

Several routes have been proposed to explain metastases to the ovary:

1. Transcoelomic dissemination with surface implantation, including metastasis through direct continuity of the primary tumor (see the chapter on peritoneal metastases);

2. Lymphatic flow metastases;
3. Blood-borne metastases.

The route by which cancer cells reach the ovaries will vary according to the primary. Multiple pathways are probably involved: direct extension by contiguity, inoculation by cells from the peritoneal fluid, passage through the Fallopian tube, retro-peritoneal and other lymphatic channels or the bloodstream (fig.4.3).

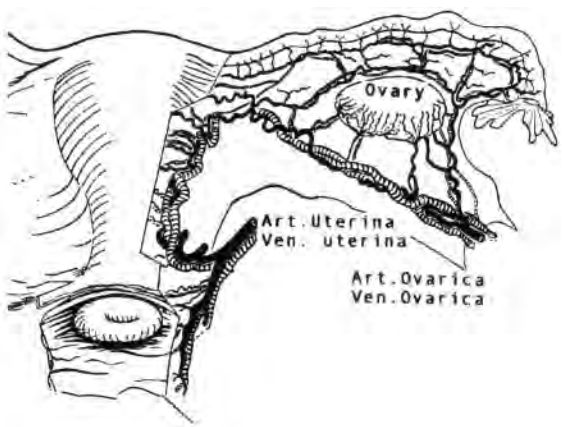

Fig. 4. 3 - Vascularization of the Ovaries

Adjacent tumors such as endometrial and colonic tumors almost certainly invade the ovaries by contiguity. Gastric carcinoma reach the ovaries through the peritoneal fluid after having come through the gastric wall, although small tumors also metastasize to the ovaries.
Retrograde lymphatic flow occurs after blocking the channels. Tumors invading the retroperitoneal nodes such as those from the upper abdominal organs and the breast reach the ovaries by this pathway, which explains the high incidence of up to 75% of bilateral involvement. Nevertheless, solitary ovarian metastases are not infrequent, confirming the likelyhood of hematogenous spread.

Investigations based on 103 patients with ovarian metastases, mainly from gastric and colonic cancers, suggests that both transcoelomic and retrograde lymphatic flow are probably responsible for the ovarian metastases. The incidence of lymphatic metastases in these patients is higher than in stage III colonic cancers (Chang et al.).
Metastatic cells first reach the stroma of the ovarian hilus, then spread to the medulla or cortex, to grow diffusely later. As cancer cells reach the capsule they rarely break or invade it. This favors the hypothesis of lymphatic spread, at least for abdominal tumors, even in the presence of intra-peritoneal lesions.

Nomenclature - Definitions

Since there may be synchronous endometrium and ovarian carcinomas, such tumors should not be regarded as metastatic. It is also difficult to assign the primary site in such cases.

Mazur et al. proposed the following criteria:
1. the ovarian lesion should be regarded as metastatic when it is small;
2. the lesion is present either at the hilar lymphatics or is a small, nodular growth at the surface of the ovary;
3. endometrial metastases are small lesions infiltrating around normal endometrial epithelium;
4. large tumors at both locations are to be excluded from the analysis and not taken in account.

Microscopic metastases in the ovaria removed at therapeutic oophorectomy will modify incidence data. This is discussed in the chapter on breast cancer.

Incidence

Several authors state that 15 to 20% of ovarian tumors are secondary. True incidence rates are not at hand. A good indication are autopsy data, but only to the extent that all cancer patients have been autopsied. One series has been reported by Fujiwara et al. (table 4.24). Of 313 women coming to autopsy for cancer, 60 or 19% had ovarian metastases. The data are relatively parallel to the clinical series, stressing the high incidence of ovarian metastases in breast, colonic and stomachal cancer.

Table 4.24 - Metastases to the Ovary
Incidence data - Autopsy series
Data by Fujiwara et al. 1955

	N	with ov.meta(%)
Extra-Abdominal		
Breast	57	13 (22.9%)
Bronchus	29	1 (3.4%)
Abdominal		
Stomach	47	18 (38.3%)
Colorectal	13	4 (30.8%)
Bile duct	31	7 (22.6%)
Pancreas	36	7 (19.4%)
Liver	37	2 (5.4%)
Kidney	6	3 ((50%))
Others	57	5 (8.8%)

Timing

The occurrence of ovarian metastases within the patient's tumor history will be variable. Quite a number are first presentation (type 1), masquerading as primary ovarian carcinomas. Several series of this type of metastases have been published (see table 4.25).

Pathology

The macroscopic aspect of ovarian metastases is variable and does not seem to correlate with the primary (Ulbright et al.). It can be either solid or cystic.
Solid tumors present having a as diffuse or as nodular surface eventually with small cysts. Cystic tumors are

Table 4.25 - Metastases to the Ovary
Primary Tumors as stated in different literature series

	Israel 1965 N=32	Greene 1969 N=64	Webb 1975 N=357	Ulbright 1984 N=29(°)(")	Mazur 1984 N=143	Demopoulos 1987 N=76	Yazigi 1989 N=29(°)(")	Petru 1992 N=82§	Ayhan 1995 N=151	Perucchini 1996 N=25
Primary										
Stomach	4	2	29	3	6	6	3	22(9)	17	7
Colon	7	14	104	9	40	12	15	23(11)	18	6
Gallbladder	1	0	0	0	0	0	0	2	0	0
Rectum	0	1	32	0	0	0	0	0	0	0
Ileum	0	0	0	0	0	0	0	0	4	0
Appendix	0	0	0	0	2	0	1	0	6	0
Breast	13(1)	27	109	7	46(*)	32	5	28(8)	27	6
Endom.	5	18	44	--	16	14	--	--	64(')	0
Cervix	1	1	10	--	14	--	--	--	4	--
Tube	1	0	9	--	--	--	--	--	--	--
Vagina	0	0	1	--	--	--	--	--	--	--
Unkn.Unspec	--	1	4	--	10	--	1	--	11	5
Other	--	--	15	--	9	12	--	--	--	--
Melanoma	--	--	--	2	--	--	--	--	--	--
Carcinoid	--	--	--	4	--	--	--	--	--	--
Bladder	--	--	--	1	--	--	--	--	--	--
Pancreas	--	--	--	2	--	--	3	7	--	1
Mesothel.	--	--	--	1	--	--	--	--	--	--
Bronchus	--	--	--	--	--	--	1	--	--	--

(°) only extragenital; (") all type 1 metastases; (*) incl.43 incidental at therapeutic oophorectomy
(§) type 1-metastases in parenthesis; (') incl. 13 myometrial sarcoma.

usually multilocular and can be divided into necrotic or non-necrotic tumors. In their series, the gastric cancers had solid, diffuse metastases, whereas lobular breast cancer, carcinoid and colonic adenocarcinomas had usually a solid nodular growth.
Cystic tumors can be mistaken for cystadenocarcinomas. Many cancers, but frequently colonic tumors give this metastatic type. Ovarian metastases have a typically the high frequency of bilateral involvement. The autopsy data of Fujiwara et al. reported bilaterality in 80% of the patients.

Young et al. have addressed the problem of differential diagnosis between metastases of tumors of the GIT, particularly those with clear cells and some ovarian cancers which also show some clear cell features. They indicate a number of characteristics to help in the diagnosis.

1. The presence of any intestinal adenocarcinoma is a clinical argument;
2. The intestinal tumor has a definite different aspect from a secondary from an ovarian carcinoma. The transmural spread of the intestinal tumor, with its association with lymph nodes, omental and peritoneal involvement are a second argument. Intestinal cancer in young women has a high frequency of ovarian metastases;
3. Bilateral involvement of the ovaries is very frequent in metastases;
4. Cystification is a well-known feature of metastatic cancer involving the ovaries, with nodularity and vascular invasion;
5. Intraluminal 'dirty necrosis' is a very useful indication of metastatic intestinal adenocarcinoma;
6. Mimicry of mucinous intestinal neoplasm with primary endometrioid carcinoma must be recognized;
7. Immunohistochemistry with several antigens can be a further way to the differentiation;
8. When the intestinal primary is not recognized or is absent, simulation of the ovarian metastases by other primary 'clear cell' ovarian cancers is to be remembered (table 4.26).

Table 4. 26 - Metastatic 'Clear Cell' Ovarian Cancers
Extragenital Cancers simulating Ovarian Epithelioma
Modified from Young et al.

Endometrioid	**Mucinous**	**Clear Cell**
Large Bowel	Large Bowel	Kidney
Biliary System	Pancreas	Large Bowel
Stomach	Stomach	Small Intest
Appendix	Biliary system	Liver
Small Intest.	Small Intest.	
Breast	Appendix	
	Bladder	
Transitional	**Serous**	
Urinary Tract	Breast	
	Intestine	

The size is smaller than 5 cm in 75% of the ovaries examined (Fujiwara et al.).
Two pathological gross findings are highly suggestive but not pathognomic of metastases. The first is the presence of multiple nodules and location on the

surface without significant involvement of the deeper parenchyma.
Cysts that on microscopic examination simulate follicles may be encountered in many metastatic tumors including gastric and intestinal carcinomas, carcinoids, pulmonary small cell carcinomas and malignant melanomas.
The different pathways are more or less correlated with the type of metastatic evolution within the ovaries (Hirano et al.). Four different patterns of ovarian involvement have been described by Hirono et al. (fig.4.4).

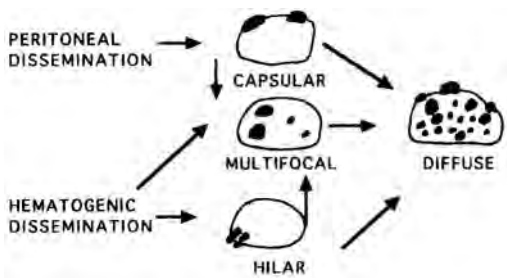

Fig.4.4 - Possible pathways of metastatic cells to the ovary and the different presentations (Modified from Hirono et al.)

To differentiate malignant metastatic from primary pseudo-mucinous or serous cystadenocarcinoma can be a challenge for the pathologist. The surgeon should report on his referral document the state of the stomach and the colon, while removing any 'metastatic' ovarian tumor (Girvin et al.).
Interesting data on the pathology of the abdomen have been reported by Ayhan et al. (table 4.27).

Table 4.27 - Metastases to the Ovary
Operative and pathology findings (N=168)
Data of Ayhan et al.1995

Finding	
Ascites	41%
Involvement of genital viscera	11
Diffuse peritoneal involvement	22
Liver involvement	6
Colon involvement	5
Unilateral Ovarian	38
Bilateral involvement	61
Retroperitoneal node positive	62

Symptoms

Ovarian masses may precede the symptoms of the primary tumors (type 1 metastases).
In fact, any adnexal mass found on clinical pelvic examination in an 'oncology patient' or symptoms of lower abdominal pain or tenderness should be suspected of being metastatic. This condition must be differentiated from a primary ovarian cancer.
Nevertheless, symptoms of an ovarian mass are not specific for a metastatic process. Details are however usually absent in the different reports. Only Yasigi et al. reported data, but only for type 1 metastases (table 4.28). This is probably not different for metastases when the primary is known.

Table 4.28 - Metastases to the Ovary
Symptomatology at presentation (N=29)
All type 1 metastases - Yazigi et al. 1989

Abdominal pain	48%
Increased girth	45%
Vaginal bleeding	10%
Amenorrhea	3%
Ascites	41%
Pelvic mass at exam.	93%
Asymptomatic	(I patient)

Diagnosis

If clinical suspicion is mandatory, a challenging responsability rests on the pathologist.
The presence of a prior or synchronous primary tumor elsewhere and the presence of extra-ovarian spread atypical for an ovarian cancer should alert the pathologist to the possibility of ovarian metastasis. The presence of pulmonary and/or hepatic metastasis without peritoneal in-volvement is uncommon for a primary ovarian cancer and rise suspicion of a metastatic proces.
The presence of a bilateral involvement is another argument for suspicion, as about three quarters of the metastases are bilateral.

At CT, ovarian metastases are indistinguishable from primary ovarian cancer (Mata et al.). The ovarian mass is mixed solid and cystic in a variable proportion. Thick walls, internal thick septa, apillary projections, irregular calcifications, contrast enhancement and extracapsular extension are observed like in primary cancers. Megibow et al. arrived at the same conclusions after review of 32 patients. Neither primary had a particular type of ovarian metastases, as the cystic, solid or mixed type occurred in all primaries.

One problem is that frequently patients with metastatic ovarian tumors are handled by different doctors at different periods of the disease process. This does not favor continuity of observation and a consequent thorough evaluation of the patient's state.

KRUKENBERG TUMORS

Originally described in 1896 by Krukenberg, this tumor type has been a matter of controversy in the literature. He originally erronously described them as ovarian sarcomas. This was refuted in 1902 by Schlagenhaufer who identified them as metastatic gastrointestinal carcinomas. In the years that followed and up to recently the term has been applied either in its most restricted way to refer to ovarian metastases of a specific histology or even loosely as ovarian metastatic carcinomas of any origin.

In 1938, Novak and Gray proposed criteria for the

diagnosis of a K.T.

1. a malignant tumor in the ovary;
2. intracellular mucin production by neoplastic signet-ring cells;
3. diffuse sarcomatoid proliferation of the ovarian stroma.

These criteria were endorsed by Woodruff and Novak in 1960 and are currently used by the WHO for the classification of K.T. (Cheung et al.).

If these criteria were to be applied, many classified as KT would be excluded. The true incidence would then be probably lower than previously supposed. Only 4 of the 53 cases metastatic to the ovary in the autopsy series of Karsh and 16 of 268 malignant ovarian tumors of Soloway et al. met the criteria.

Although the term is still used (mainly by surgeons) for any metastatic tumor of the ovaries, the term should no longer be used. This brings a bias in the literature series of metastatic tumors, both being labeled many times as Krukenberg tumors including breast and other primaries.

It is nevertheless striking that the mean age at which the K.T. occurs is relatively young, and the metastasis is either bilateral, or very frequently at the right. When bilateral, the right ovary is the largest, sometimes reaching 10 to 15 cm (Wolff).

Hormonal Syndromes

Clinically evident hormonal syndromes in patients with ovarian metastases are very rare (table 4.29).This is a very puzzling situation, as the primary is commonly a non-endocrine tumor. It appears likely that the presence of foreign metastatic cells induces production of hormones, estrogens, androgens or progestogens. In one, the observation of virilization of the fetus prompted the diagnosis of ovarian metastases.

Table 4.29 - Hormonal Secretion in Ovarian Metastases Cases Reported in the literature

Ober 1962	Sigmoid cancer	Hirsutism
Connor 1968	Gastric cancer	Virilization in pregnancy
Bell 1977	(report not available)	Virilization of fetus
Jolles 1985	Colon cancer	Progest. Breast tenderness
Brennecke 1986	Cecum canc	Estrog. Uterine bleeding
Caron 1990	Breast cancer	Virilization
Lemahieu 2000	Colon	Estrogen : Breast tenderness

METASTASES to the UTERUS

When considering uterine metastases, one must differentiate metastases in the endometrium, the myometrium and the cervix. The literature is, however, somewhat confusing, as some reports only consider the uterus as a whole.

METASTASES to the CERVIX UTERI

Pathways

As with many other organs, the cervix uteri can be either invaded from a neighbouring tumor or colonized by hematogenous spread (table 4.30). The latter is a rare event, while an extension from endometrial carcinoma is a common occurrence classified as stage II. We will not discuss this problem although some authors are adamant that uterine cervix extension from endometrial carcinoma should be viewed as metastatic. It is very difficult to distinguish mucosal spread from a distinct cervical location.

Table 4.31 - Metastases to the Cervix Uteri - Literature data

Author	Esposito 1965 N=80(*)	Way 1980 N=8	Zhang 1983 N=6	Korhonen 1984 N=14(°)	Mazur 1984 N=12	Lemoine 1986 N=33	Mulvany 1996 N=6(§)	Gupta 1999 N=33(°°)	TOTAL
Primary									
Breast	41	1	--	1	--	4(1)	--	6	53 (28%)
Stomach	23	2(1)	5(4)	--	1(1)	5	--	--	36 (19%)
Lung(Bronchus)	4	--	--	--	1(1)(+)	--	--	1	6
Kidney	2	--	--	--	--	2(1)	--	--	4
Ovary	--	3(2)	--	6	7(1)	12(1)	3(')	14	45 (24%)
Tube	--	1(1)	--	2	--	--	1	1	5
Recto-Colon	6	1(1)	1	5	2(1)	10	1	6	32 (17%)
Liver	1	--	--	--	--	--	--	--	1
Gallbladder	1	--	--	--	--	--	--	--	1
Skin Melanoma	--	--	--	--	1(1)	--	--	--	1
Urin.Bladder	--	--	--	--	--	--	1(")	1	2
TOTAL	**80**	**8(5)**	**6(4)**	**14**	**12(5)**	**33(3)**	**6**	**33**	**187 (17)**

() Number in parenthesis are type 1 or revealing metastases; (*) Review of literature and 2 own cases;
(°) excluding 31 endometrial carcinomas; (§) excluding 10 endometrial carcinomas;
(+) histology not specified; (') all endometrioid carcinomas; (") urachal adenocarcinoma
(°°) diagnosis of malignancy in PAP-smear, +1 pancreas, 2 unclear cases and one lymphoma

Table 4.30 - Metastases to the Cervix Uteri
Pathways

1. Hematogenous
2. Retrograde venous flow, via ovarian vein to ovary, uterus, vagina
3. Retrograde lymphatic spread (as discussed further)

Indeed, epidermoid and other epithelial metastatic tumors have to be distinguished from metastatic adenocarcinoma as the latter could be primary adenocarcinomas of the cervix proper. As the lymphatics of the uterus, the salpinx and the ovaries are confluent, retro-grade lymphatic dissemination can be postulated and is likely responsible for primaries in the genitourinary system. Hematogenous spread is obvious for more distant primaries (Mac Comas et al.).
The infrequent occurrence can be attributed to several factors (table 4.32).

Table 4.32- Metastasis to the Uterine Cervix
Reasons for Rarity (Nakagami et al.)

1. High fibrous tissue content of the cervix
2. Small tissue volume with low vascularity
3. Lymphatics draining away from cervix
4. Difficult differential diagnosis between primary and metastatic adenocarcinoma
5. Screening of cervix rarely done in follow-up

Incidence

In a series of 23,869 autopsies (gender not stated !), DiBonito et al. found 20 patients with true metastasis in the uterus. Only 1 had a single metastasis in the cervix(from a breast cancer, and two others had a mixed cervix-myometrium metastasis, one from a breast and one from a bronchial cancer.
A survey of the few cases reported shows that almost all cases are adenocarcinomas, although histology is not always stated appropriately. All series are clinical. One remarkable fact is that several metastatic tumors, overall seventeen or 10%, are type 1 metastases. We have grouped the literature reviewing all the series in table 4.31. It shows that breast, stomach and ovarian cancers are the most cited primaries. Peculiar is the presence of 4 tubal cancers and the progressive increase in ovarian primaries.
Additional to these cases are reports on bronchial adenocarcinomas, breast, stomach and renal cancers metastatic to the uterine cervix.

Symptoms

The symptoms of these metastases are no different to those of primary cervical (adenocarcinoma) tumors. Vaginal bleeding is the predominant symptomatology.

Diagnosis

Biopsy-histology will usually reveal the metastatic nature, but it may frequently be difficult, especially when the primary is unknown.
A lesson is that when an adnexal mass is palpated in the pelvis in a patient with a cervical tumor, the diagnosis of a second primary or of the primary in the ovary should be taken in account.
Occasionally positive PAP smears have been obtained which show adenocarcinoma cells without an obvious cervical cancer. This situation is described in a few case-reports, as was reviewed by Jaluvka et al. As shown in the data on table 4.31, 15 of the 34 retrieved cases were from a stomachal cancer and 9 from a sigmoidal cancer. In 8 of the patients ovarian metastases were also present, presumably due to spread of cells along the tube and the uterine cavity.

METASTASES to the MYOMETRIUM and/or the ENDOMETRIUM

The few reports that have addressed this site do not clearly separate the two sites. In many patients both structures and even all layers are involved.

Pathways

Pure hematogenous spread to the endometrium is not common. Of course, we exclude here, the situations with contiguous invasion of the myo- and/or endometrium by cancers of the sigmoid, rectum, ovaries and urinary bladder. We also exclude any discussion of the extension from cervical carcinoma, in fact not a metastasis but at all invasive spread (fig.4.5).

Incidence

Only few reports have appeared (table 4.33). Of the 39 primary tumors mentioned in these series, 38 or 30% concern a breast cancer.
The data from the autopsy series of Kumar N. show that 43/63 or 68% were only found at autopsy. It is not stated if these patients had pre-mortem symptoms.

Table 4.33 - Metastases to the Uterus
Literature series

	Kjaer 1972	Kumar 1982	N.(+) 1982	Kumar A. 1983(+)	Mazur 1984
Primary		Aut(°).	Surg.		
Breast	4	20	7(1)	5	2
Stomach	1	6	1(1)	3(2)	1
Colon	--	3	8(1)	2	2
Pancreas	--	6	1(1)	--	--
Gallbl.	--	3	0	--	--
Lung	--	2	1(1)	1(1)	--
Ovary	--	--	--	--	5
Tube	--	--	--	--	3
Melanoma	--	2	0	--	--
Urin.Bladder	--	1	1	--	--
Thyroid	--	0	1	--	--
Appendix	--	--	--	--	1

() cases presenting as type 1-metastases
(+) endometrium and myometrium metastases
(°) autopsy

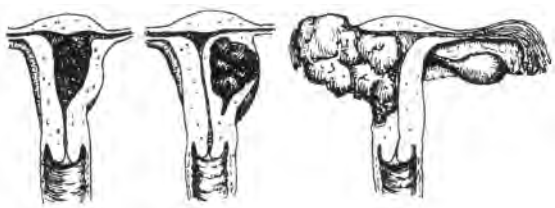

Fig. 4.5 - Left: Metastases to the endometrium (mucosal),; Middle: intramural or myometrial metastasis and Right: infiltration in the uterus from a neighbouring tumor.

The same authors are the only authors differentiating between endometrial and myometrial metastases. Of 52 cases where it had been determined, 33 had myometrial invasion only, a metastatic type not reported elsewhere. The contributing primaries are not mentioned. Solely endometrial metastases were present in only 2 cases, while 17 had both metastatic sites. This results in a figure of 96% myometrial metastases.
Type 1-or revealing metastases are actually reported in 5 cases of Kumar N. and 3 cases of Kumar A. If only these two series are taken into account, in 8 of the 74 or more than 10%, the metastasis was the first sign.
Other such patients have been reported for breast, bronchial and other cancers.
There were 13 cases of metastases within a uterine leiomyoma in the series of Kumar N.. Six of them were restricted to benign tumors. This is discussed later (Chapter 7).
In the previously cited series of DiBonito et al., 19 of the 20 uterine metastases were in the myometrium. It concerned 11 breast cancers, 3 pancreas, 2 stomach and the colon, and 1 gallbladder cancer.

Symptoms

To the extent that the reports have enough details given, metrorrhagia is the main presenting symptom. Anemia and pelvic discomfort has also been reported.

Diagnosis

Curetting and/or biopsy is the best way obtaining diagnosis, but in several situations, pathology of the resected uterus has lead to diagnosis. We stress again that in many patients, it was only found at autopsy.

METASTASES to the VAGINA

Metastases in the vagina are a rare event. Nevertheless their occurrence seems to have a particular significance to the pathology of some tumors.
Invasion from tumors of neighbouring organs such as rectum and urinary bladder is, of course, not to be withhold as a metastasis.

Pathways

Several routes have been implicated as explaining this site for metastases. While hematogeneous spread with lodging of cancer cells in the mucosa is plausible, some aspects of the pathology data call for another more plausible pathway.

Since vaginal metastases originate mainly (about 75%) from left-sided kidney tumors, retrograd venous flow is the now most accepted mechanism.
Retrograde flow from the left renal vein to the left ovarian vein, the ovarian plexus and the ureterovaginal plexus can readily explain its occurrence. Right-sided kidney tumors with vaginal metastases have been reported, but a short-circuit of the right vein with the left ovarian is a probable cause (fig.4.6).
Several type 1 or revealing vaginal metastases have been reported for kidney cancers.

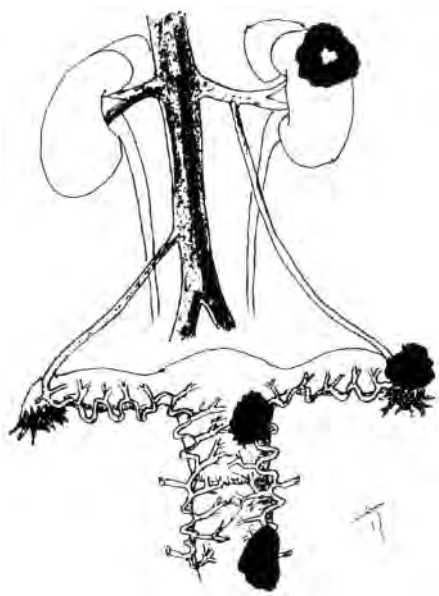

Fig.4.6 - Connection between the renal vein and the pelvic venous plexus, as an explanation for the retrograd blood flow for metastatic spread of renal tumors into the ovary, the uterus and the vagina

Retrograd lymphatic flow is not a likely cause as in most operated or autopsied cases of renal cancer, there were no retroperitoneal metastatic nodes found.
Spread from the right kidney to the vagina would seem less frequent, although flow from the right renal vein to the inferior vena cava and retrograde via the right ovarian vein may constitute a possible route (Sogani et al.).

The presence of a tumor thrombus in the right vein may also cause extensive venous anastomoses, creating conditions for the retrograde spread of metastatic cells (Stefani et al.).

Incidence

Incidence data are not available, as review on vaginal metastases are not at hand. Up to 1970, 44 cases have been reported.
According to the number of literature case reports, the kidney is the most frequent cited primary. A lot of them are even type 1 metastases (revealing). Breast cancer is also a frequent primary.
Many vaginal metastases have been reported for endometrial carcinoma, but contiguous spread is not always distinguished from true metastatic nodules.

Symptoms

Vaginal bleeding is the most frequent presenting sign, itching or even protuding masses have been described.

Pathology

As far as the metastases of renal carcinoma are concerned, the vaginal metastases are almost all in the lower third and anterior wall. Histology can reveal the exact nature when the primary is not known.
According to several authors, isolated metastases in the vagina from renal tumors are two to three times more frequent than multiple ones. Some authors even state that the site of the metastases is identical with the side of the primary in the kidney (Ovesen et al.).

Diagnosis

Clinical examination, biopsy and the obtained histology will lead to diagnosis.

METASTASES to the VULVA

Pathways

Retrograde venous or lymphatic spread from the pelvic tumor is a logical explanation. Hematogenous spread can explain a metastases from the breast, but a renal tumor could metastasize along a venous reflux route, as discussedin relation to the vaginal metastases.

Incidence

Metastases in the vulva are rare. The literature is relatively silent. On this subject, in 1973, Dehner found over a period of 15 years on 262 patients with vulvar tumors, of whom 22 (8%) were metastatic tumors. Ten were from cervical carcinoma and 8 from other gynecologic tumors. Only 4 were from an extrapelvic tumor.
A few case reports have appeared on breast cancer (7), kidney (4) and one of a stomach cancer. In their survey on metastases to the female genitalia, Mazur et al. found only one case from a breast and one from a kidney cancer. Fourteen cases were from a genital tumor (table 4.34). Cohen reported on one breast cancer, one renal carcinoma and one malignant melanoma.

Table 4.34 - Metastases to the Vulva
Primary Tumors - Literature Data

	Dehner 1973	Mazur 1984
Cervix Uteri	10 cases	7
Endometrium	4	6
Ovary	1	1
Urethra	2	--
Vagina	1	--
Kidney	2 cases	1
Breast	1	1
(Lymphoma	1)	

Pathology

As a rule, the histology is the same for the primary and the secondary. The literature, however, does not always report the histology type.
Compared with vaginal metastases, vulvar metastases are more frequent from distant tumors and are usually associated with widespread disease (Cohen et al.).

Symptoms

The symptoms described in the case reports are local bleeding, pruritus, a painless nodule, and only rarely an ulcerated one. The vulvar nodule can be present at dia-gnosis or occur several months later. We think that most primaries were at an advanced stage.

Diagnosis

Clinical inspection and examination with biopsy of the lesion.

METASTASES to the CLITORIS

As can be expected the clitoris may be invaded by neighbouring cancers from the vulva, the vagina and the bladder, by contiguous growth.
In the literature, we found three references concerning real clitoral metastases. It concerned one bladder tumor, one from a stomachal and one from a rectal cancer.
The presenting symptomatology is local severe vulvar pain.

METASTASES to UTERINE LEIOMYOMA

As will be discussed further in Chapter 7, metastases may occur in benign or malignant tumors, several cases of metastasis within a uterine leimomyoma, either solely or simultaneous with uterine metastases, have been reported in the literature. Of the 63 cases of metastases in the uterus, metastases in a leiomyoma was seen in 13 cases (20%)! In six of them the metastasis was present only in the myoma (Kumar N.) Of the 11 patients reported with uterine metastases, 3

had a leiomyoma metastasis, or 30%. This is quite remarkable.

Table 4.35 - Metastases to Uterine Leiomyoma Primaries (Literature survey)

Breast cancer	31 cases (69%)
Bronchus/lung	5 cases
Stomach cancer	4 cases
Pancreas	3 cases
Gallbladder	1 case
Melanoma	1 case

Darai et al. reported a case with adenocarcinoma metastases from an unknown or unfound primary.
Reviewing the literature in 1997, they found 12 other cases apart from the Kumar series.
The main primary concerns breast cancer, totalling 31 of the 45 cases or 68% (table 4.35). Only Minelli et al. reported a case with revealing metastases from a breast cancer (type 1).

METASTASES to the PLACENTA

Malignant neoplasms are less frequent in women of childbearing age than at later ages. The incidence of malignant tumors during pregnancy is not uncommon, but the involvement of the placenta and/or of the fetus is rare.
Some have estimated the incidence at 1/1500 pregnancies, but data are insufficient for definite conclusion. There is probably some underreporting, as the placenta is not examined systematically, even when grossly enlarged at stillbirths and hydrops fetalis.

Table 4. 36 - Metastases to the Placenta Literature Review by Dildy et al., by Elthorky et al. and the author

Melanoma	24 cases
Breast Cancer	10
Leukemia-Lymphoma	9
Bronchus (all hist.)	8
Sarcoma (incl.one orbit)	4
Stomach	2
Pancreas	2
Head and Neck	2
And 1 case from liver, adrenal, rectum, medulloblastoma, and one unknown (undifferentiated)	

Pathways

It is obvious that the rich vascularisation of the placenta represents a potential site for retaining circulating tumor cells. Only one case of cervix uteri cancer can be retained for a contiguous invasion.

Primaries

We were able to find 67 cases reported in the literature (table 4.36). The majority concerns malignant melanoma (36%), a neoplasms more frequent in this age group. The literature review is based on the two extensive ones by Dildy et al. and by Elthorky et al.
Six cases were reported since then.
Reviewing the literature in 1997, Ackerman et al. retrieved other features as well and remarked that in half of the women, the malignancy was unknown before pregnancy.

Pathology

In a large number, if not all, microscopic nests of malignant cells can be seen in the intervillous spaces. According to Ackerman et al., half of the placentas showed visible tumor nodules. Extensive involvement was seen in 10 cases (Eltorky et al.).

Symptomatology

As far as can be deduced from the reports, most are asymptomatic, but when the placenta becomes severely involved, placental insufficiency occurs with abortion. It is not unlikely that many 'vague' complaints such as backache, fatigue and abdominal discomfort are dismissed and related to the pregnancy, postponing the definite diagnosis. Present routine echography during pregnancy will probably allow an earlier diagnosis, but it has not been reported yet.

Metastases from a Congenital Fetal Malignancy

Up to 1980, when Perkins et al. reviewed the literature while reporting of a case of placental infiltration due to congenital neuroblastoma, three fatal fetal neoplasms were known to have spread to the placenta, leukemia, giant pigmented nevus and neuroblastoma. Later Lynn et al. retrieved 10 cases.
We found reported cases of metastases to the placenta from other congenital foetal neoplasms as one hepatoblastoma and one hemangioblastoma. In addition, a congenital malignancy should be considered in the differential diagnosis of an abnormally large placenta (Smith et al.).

METASTASES to the FETUS

Fetal involvement was documented in only 13 of the above-mentioned cases or 20% (Dildy et al.). Half of the fetuses were invaded by a malignant melanoma and 4 by a lymphomatous malignancy. The low incidence of the fetal involvement can be ascribed to

1. the strict mechanical separation between maternal and fetal circulation;
2. an inherent resistance of the trophoblast to tumor invasion;
3. a possible immune reaction with rejection of the invading tumor cells.

In every pregnant oncology patient delivering a child, the placenta should be carefully examined at histology, with special attention to the intervillous and

intravillous spaces and the capillaries of the placenta and of the fetus.

Bibliometry

The number of references - articles - on metastases in each part of the system should more or less reflect the respective incidence of metastases in that site. The number of references is not equal to the number of cases (table 4.37).
These data are, of course, only indicative of the relative incidence of concerned primaries. There are many articles reviewing more than one primary.
Nevertheless, it can be said that overall breast and kidney tumors are the most frequent primary. One unexpected is the presence of stomachal cancer as another primary. Their widespread metastatic pattern is well-known and corroborates relatively well with these data.

Table 4.37 - Metastases ito the UrogenitalTract
The most frequent Primary according to Site

Urinary system:	
Kidney: 138 ref.	Bronchus(18), thyroid (13)
Ureter: 63	Breast (13), kidney 15)
Urinary Bladder: 56	Kidney (21), breast (7)
Male Genital System:	
Testis 116 ref.	Prostate (35), colon (16), Kidney (13), stomach (8)
Prostate: 15	Bronchus (2)
Epididymis: 38	Prostate (13)
Spermatic Cord: 23	Stomach (6), prostate (4)
Penis: 137	Prostate (28), Urinary bladder (20), Kidney (13)
Female Genital system	
Ovary: 276 ref.	Colon (46), breast (28), cervix uteri (22)
Cervix Uteri: 47	Stomach (11), breast (12)
Endometrium : 31	Breast (11)
Uterus :49	Breast (24)
Vagina: 75	Kidney (39), Endometrium (14),
Vulva: 24	Breast (7), kidney (4)

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Caution: References are given for documentary purposes. Not all have been reviewed or used in the redaction of the text. We do not claim completeness of data. The references are as much as possible grouped per subject heading.

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5

METASTASES to the CENTRAL NERVOUS SYSTEM

Brain metastases originate from tumors outside the brain. They are the most frequent neurological complication of malignant tumors, aside from toxic or paraneoplastic phenomena. There seems to have been an increase in their incidence over the last five to six decades, possibly due to the increasing length of survival obtained from the treatment of several tumors.

TERMINOLOGY

The term 'single' metastasis implies only one 'visible' metastasis, without consideration of any metastatic site elsewhere in the body. A 'solitary' metastasis, however, implies the absence of any other site within the body. When multiple metastases are said to be present, the presence of metastases elsewhere is almost never taken into account, although it could possibly have implications for the treatment policy and prognosis (table 5.1).

Table 5. 1 - Central Nervous System Metastases Definitions

Single	: only one metastasis in cerebrum
Solitary	: no other metastases elsewhere
Multiple	: many different all over the brain

The statement of single or multiple correlates in fact with the ability of the diagnostic (imaging) methods. Intracranial metastases imply the possibility of meningeal and intracerebral metastases, although the former are much less frequent: about 4 to 6% of oncology patients, in half of them it will be the only pathology.

The metastases in the central nervous system (CNS) can be classified as in table 5.2. The different types have clinical and therapeutic implications and will be discussed in turn.

The relative frequency of this metastatic location correlates roughly with the relative volume of brain parts and their blood flow. The cerebral hemispheres will contain about 80% of the metastases, while 15% will be found within the cerebellum and 5% in the brain stem. Multiple locations within the same patient are, however, not uncommon (table 5.3).

Table 5.2 Central Nervous System Metastases Classification (modified from Posner)

A. Intracranial
   1. Intracerebral, single or multiple
   2. Subdural, with or without effusion.
   3. Extradural, with or without compression of sagittal sinus.

B. Leptomeningeal metastases
   1. Diffuse or widespread - multifocal
   2. Focal to base of brain or spinal meninges
   3. With parenchymal invasion in brain or cord

C. Metastases within vertebral canal
   1. Extradural: spinal cord compression
   2. Intramedullary: spinal cord invasion
   3. Vertebral only: bone metastases with possible spinal cord compression.
   4. Brain stem metastases

Table 5.3 Central Nervous System Metastases
Relative Incidence of different location
Clinical and autopsy data (Chason et al.)

Cerebral Hemisphere	75%
Leptomeningeal metastases (focal 50%, carcinomatosis 8%)	58%
Cerebellum	31%
Internal dura	20%
Brain stem	7%
Ependyma	10%

(°) several patients had metastases at different sites.

CEREBRAL METASTASES

Incidence

As we will see, several brain metastases are asymptomatic and found only at autopsy, so that data from clinical studies and autopsies will differ. In general terms, at least 20% of oncology patients will present with any CNS metastases during their life-time. The present refinement and higher sensitivity of the imaging methods also allows a much better detection of cerebral metastases.

A study dating back to 1972 concluded to an annual incidence of 11.1 per 100,000 population. A later one found that primary and secundary brain tumors can be assumed to have the same incidence (O'Neill et al.). According to Posner et al., 15% of all patients had at autopsy brain and other metastases and 9% only brain metastases.

In most if not all papers on cerebral metastases, the relative distribution of the source of the metastases is reported. The amount of metastases from bronchial cancers is about one-third of all patients with brain metastases, but the distribution may differ according to the discipline of the group reporting. A thoracic surgery department will almost never include breast cancer patients while a substantial number will be present in reports from oncology departments.

Data from large autopsy series allow to obtain data on the relative incidence of brain metastases from the different primaries (table 5.4).
It is obvious from these data that bronchial and mammary cancers, (both 'thoracal' tumors), have the highest incidence of cerebral metastases at the end of their evolution between 25 and 35% while all other primaries have a much lower rate, except for urinary tumors (up to 17%). Skin melanoma, frequently only mentioned as skin tumors in the various reports, has the highest incidence, due probably to its peculiar cellular characteristics, its own 'seed-and-soil' properties and well-known high metastatic rate.

A recent review on incidence data was published by Counsell et al. based on CT or autopsy studies. From a number of data, the incidence of brain metastases ranges between 2.8 and 16.0 per 100,000 per year, due probably to methodology differences, but this is difficult to verify. The relative incidence of secondaries vs. total brain 'tumors' varies between 20 to 48%, probably depending on the type of population studied (table 5.5).

Table 5.5 - Incidence data of Metastases to the Brain
Literature Review by Counsell et al. 1998

Country	Percent of Brain 'Tumors'	Metastases Crude Incidence Rate
Iceland	21%	2.8/100.000/year
Carlisle	45%	5.4
Jyväskyla (S)	20%	3.4
Valle d'Aosta	38%	16.0
Lothian	48%	14.3

Pathways

Malignant metastatic cells reach the brain through arterial circulation and originate from the lung, since the cerebral arteries branch directly onto the aortic arch. This explains the high incidence of bronchial primaries as source of metastases even as a first presentation (type 1), while secundary lung metastases are probably the last step in the metastatic process from extra-pulmonary malignancies. In a limited number of cases, the vertebral venous system can be the pathway for any subdural location (see further) (Batson's plexus, discussed in Chapter 7).

Pathology

The clinical symptoms of brain metastases (discussed later) derive from a number of mechanisms which impair the normal function of the brain.

Table 5.4 - Cerebral Metastases
Involved Primaries - Autopsy Data of Pickren et al. (N=10.916 patients, 1983)

Primary	N	Cerebrum	Cerebellum	Pons	Medulla	Ratio Cerebr/Cerebell
Bronchus	1,440	22.4	10.9	2.4	1.7	2.1
Skin(')	440	29.8	14.1	5.2	2.7	2.1
Breast	1,067	14.5	9.8	2.2	1.3	1.5
Soft tissue and bone	116	7.8	0.9	0	0.9	9.0
Kidney - ureter	277	9.8	2.58	0.4	0.4	3.9
Testis	121	19.0	6.6	0	0	2.9
Bladder - ureter	355	2.3	0.9	0.3	0.6	2.7
Endocrine glands	188	5.3	2.1	0	0	2.5
Unknown	136	20.6	8.8	1.5	0	2.3
Digestive system	2,281	0.03	0.01	0	0	2.2
Female genitalia	1,132	0.03	0.02	0	0	2.1
Miscellaneous	2,054	0.04	0.02	0.01	0.01	2.5
Whole cohort	10,916	9.3	4.6	1.4	1.1	2.0

The presence of a growing cellular mass within the closed cranial box will profoundly alter the finely tuned metabolic and homeostatic mechanism of the cerebral cortex. Four interdependent mechanisms can be observed (table 5.6).

Table 5.6 - Cerebral Metastases Pathophysiology

1. Mechanical distortion and displacement
2. Increase in intracranial pressure, resulting in decrease of cerebral blood flow
3. Propagation of vasogenic cerebral edema
4. Disturbance of metabolic energy process

At the microscopic level, several modifications have been described, relating eitherto the consequences of the tumoral proliferation or to a reactive 'inflammatory' mechanism to the presence of a strange tissue.
Because of vascular permeability changes, one vasogenic reaction is the leakage of proteins from microvessels, causing a pronounced edema. This results in an increased intracranial pressure, but also in a modification or rather a disturbance of the microcirculation with its influence on the brain metabolism. Vessel walls are indeed described as modified with openings in the endothelial lining. The growth of the tumor also distends axons, stretching them and causing membrane injuries around the metastases. Astrocytic reactions and astrocytosis, with changes in microglial cells, can be seen in large amounts around the metastases. The microglial cells are enlarged, have plump cell processes and are distributed even far away from the center of the metastases (Zhang et al.).

In a series of 53 patients with extracranial primaries, Goertchen et al. found in 16 patients, or 30%, only microscopic metastases in various sites, after application of immunohistochemistry in six different regions of the brain. The leptomeningeal membrane was most frequently involved.

The macroscopic aspects of the cerebral metastases correlate partially with the primary (Ferrozzi et al., table 5.7).

Table 5. 7 - Cerebral Metastases Structural Characteristics and Primary Data from Ferrozzi et al.

Calcified	Hemorrhagic	Cystic-Pseudocyst
GIT mucinous	Melanoma	Bronchus
Ovarium	Kidney	Ovary
Ser. papill. or endom.	Breast	Colon
Osteosarcoma	Choriocarcinoma	
Thyroid Medullary	Thyroid	
Bronchus		

Site

At the microscopic level, the metastases within the brain are usually situated in the gray-white junction zone. This is due probably to the narrowing of the blood vessels, forming a trap for the cellular emboli.
As the size of the blood vessels become smaller at the transition between white and gray matter, the cells will be trapped at the area just beneath the gray-white junction (Patchell). They are more frequent at the terminal 'watershed areas', the zone between the territories of the different major vessels irrigating the cerebral hemispheres.
This is nicely demonstrated by Kindt (fig.5.1). While the primary tumors are distributed relatively randomly over the hemispheres, the metastases tend to locate along the sylvian fissure in the region of the junction of the temporal, parietal and occipital lobes.

A study of the vascular distribution revealed that in the anatomic watershed areas, the distal fields contained 37% of the metastases within an area representing only 29% of the surface areas (Delattre et al.).

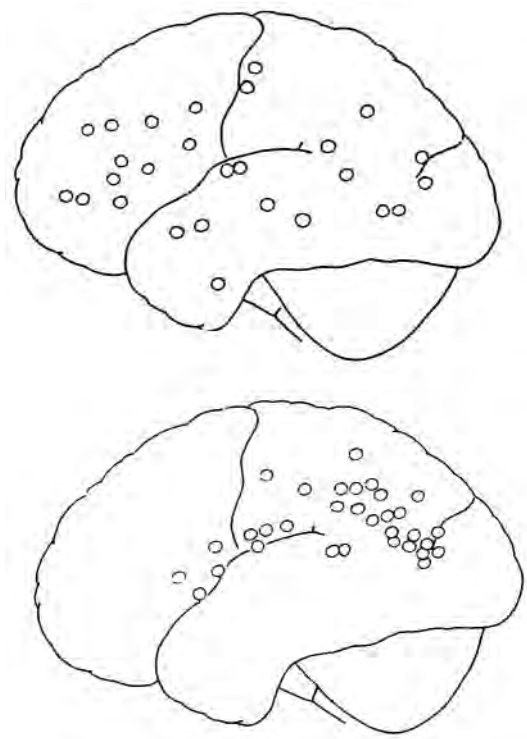

Fig. 5.1 - Comparative localisation between (above) primary (astrocytoma) tumor of the brain and (below) secundary metastatic tumors (Kindt)

This non-random pattern of distribution of the metastases throughout the hemispheres as been addressed by Hwang et al. They examined the CT-images of 100 patients and ascribed them to the major cerebrovascular zones (fig.5.2).
Border zones or watershed areas are formed by the terminal capillary beds of cerebral arteries.
The different zones are:
1. the anterior border zone, situated between the supply territories of the anterior and the middle cerebral

artery, including the centrum semi-ovale and the corona radiata;
2. The posterior border zone situated between the supply territories of the middle and posterior cerebral artery. This zone lies between the parietal and occipital lobe, inclusing the triple vessel border zone between the medial and the other parts of the temporal lobe;
3. The subcortical zone, located in the deep white matter between
- the territory of deep perforators, including Huebner's artery and the anterior striate branch of the ACA, the lenticulo-striate arteries of MCA and the anterior chorodial artery of the internal carotid,
- the vascular territory of superficial perforators, the white matter medullary branches of the MCA.
The anatomical structures include the white matter of the corona radiata and the extreme lateral portions of the basal ganglia. The area is more a junctional zone between the two terminal networks than a watershed area.
4. The cerebellar border zone is the area of blood supply overlapping the posterior inferior cerebellar artery, the superior cerebellar artery, and between the first and the anterior cerebellar artery.

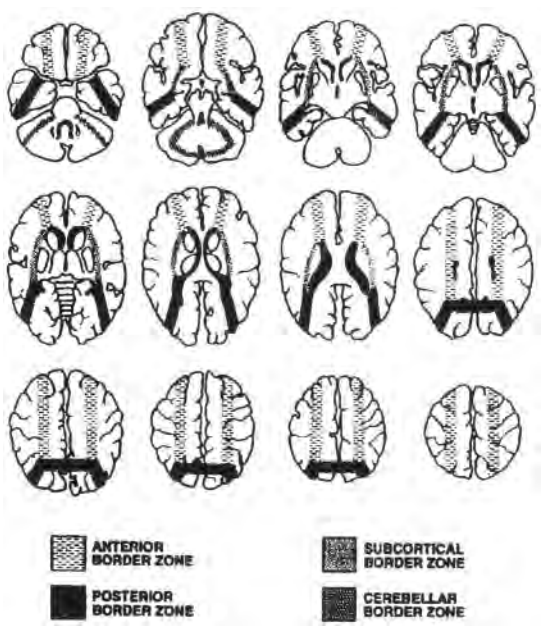

Fig.5.2 - The major cerebrovascular zones, as delineated by Hwang et al.

Of the 210 metastases, the border zones were the preferred sites in 62%, although it can be estimated to represent only 29% of the surface. Further data are shown in fig.5.3.
The gray and white matter junction was the preferred site of 64% of the lesions (fig.5.4).
The estimated mean number at the gray and white matter junction was 3.48 times greater than the estimated mean number of tumors in the gray matter and 5.37 times the estimated number in the white matter. The number in the border zones was 86% greater than the estimated number into non-border zones.
These data support the notion that tumor emboli pass along the arterial tree as far as distally as their size permits (border zones) or lodge in the region with sudden reduction in vascular caliber (gray-white matter junction).

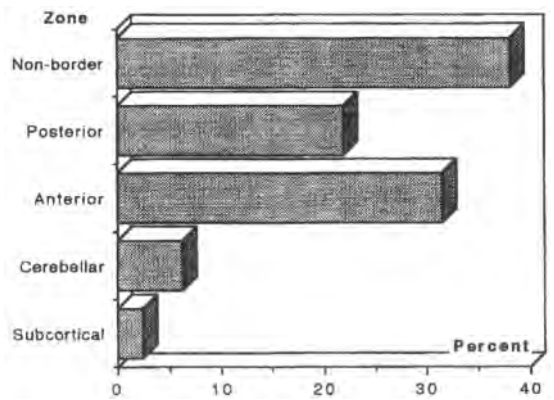

Fig.5.3 - Distribution of metastases within the different border zones (N=210 lesions) (drawn from data of Hwang et al.)

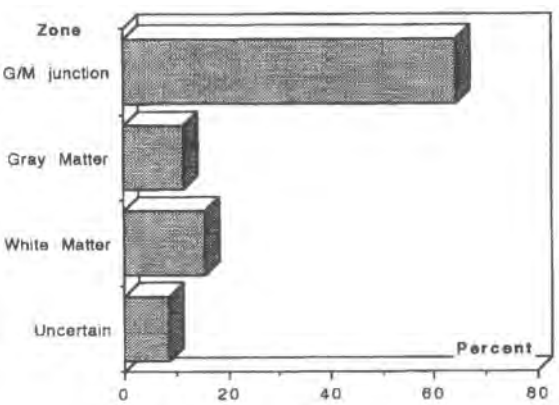

Fig.5.4 - Distribution of metastases within the different gray or white matter (N=210 lesions) (drawn from data of Hwang et al.)

There is indeed a rather sudden narrowing of the diameter of the arterioles supplying the cerebral cortex when they enter the white matter. The junction region between gray and white matter is most probably the impact site of the tumor emboli.
The incidence of brain metastases according to anatomic site (lobe or structure) is relatively well documented. It would appear that frontal and parietal lobe account for about half of the metastases (table 5.8). Only a few authors have tried to correlate the site with the type of the primary (Fig.5.6 - Berlit et al). There are apparently no significant differences, except a possible deficit of frontal metastases in kidney cancers.

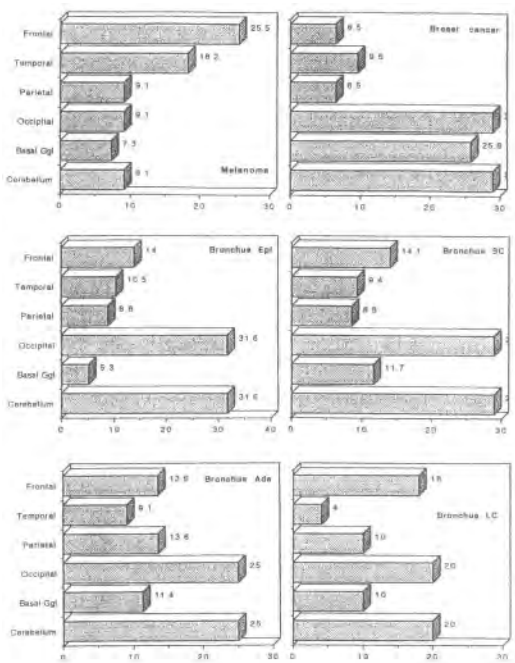

Fig.5.5 - Distribution of metastases within the CNS according to primary. Redrawn from data of Graf et al.

Reviewing 15000 consecutive autopsies at the university hospital, Graf et al. found 237 patients or 1.6% with brain metastases. The relative frequency of brain metastases as a percentage of metastases in a certain anatomical region out of all brain metastases of a particular primary is given on fig.5.5. Metastases of malignant melanoma are found predominantly in the temporal and frontal lobes and of breast cancer in the basal ganglia. In the occipital lobe, large cell bronchus metastases are most frequent, while squamous cell cancer has a predilection for the cerebellum. Small cell carcinoma metastasizes evenly all over the brain.

Egawa et al. reported on 254 patients with cerebral metastases treated by radiotherapy. They differentiated site and multiplicity according to primary (table 5.12).
An often referred to study showed an overrepresentation of fossa posterior (cerebellar) metastases, but concerned only 15 patients with prostate and uterine tumors (Delattre et al.).

Although the data are somewhat troubling, it seems that the highest incidence of solitary metastases occurs in the occipital and parietal regions. Data for other cancers are flawed by the low number of cases.

More recent interesting data have been published by Nussbaum et al. Unfortunately, they did not correlate site with the type of primary (table 5.9).
Some data from larger literature series are grouped on table 5.8.

Table 5. 9 - Metastases to the CNS
Data on site from Nussbaum et al. N=729

Single (N=384)		Multiple (N=345)	
Frontal	19%	Cerebrum	33%
Parietal	13%	Cerebr. & Cerebell	12%
Occipital	6%	Cerebellum	1%
Temporal	5%	Brain Stem	1%
Cerebellum	10%		
Brain Stem	1%		

Table 5.8 - Cerebral Metastases
Anatomic site distribution (Literature data)

Author	Brady	Pagès	Egawa (RT-study)		Delattre	Nussbaum	Salvati
	1974	1987	1986		1988	1996	1995
	All	All	Solit.	Mult.	All	All	Solitary (type 1)
	N=135	N=94	N=93	N=275	N=256	N=729	N=100
Site							
Parietal	31.6%	22.3%	23.7%	22.5%	19%	24.2%	24%
Frontal	20.0	30.0	6.5	21.5	21	35.4	25
Fronto-Parietal	10.4	---	4.3	1.8	---	---	---
Temporal	7.4	11.7	10.8	12.4	10.5	8.6	14
Parieto-Occip.	4.4	---	4.3	5.5	19.0	---	---
Parieto-Tempor.	4.4	---	2.2	2.2	---	---	---
Occipital	---	23.4	23.7	24.0	15.0	10.9	11

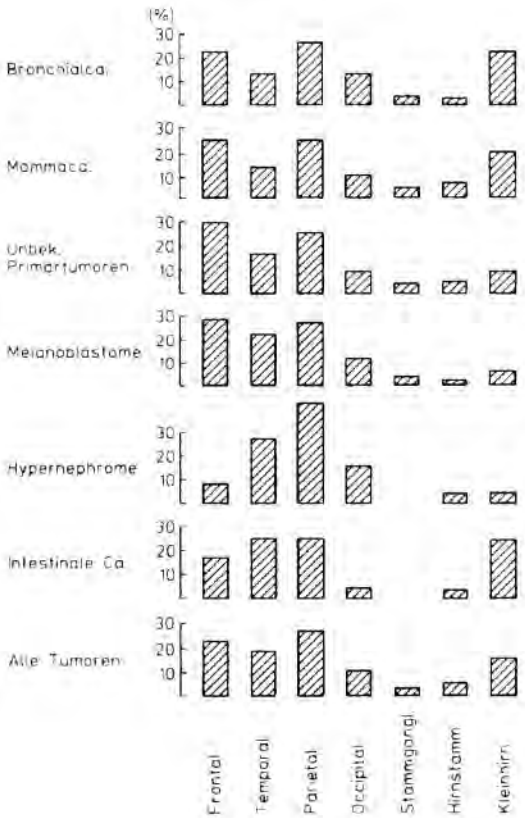

Fig.5.6 - Anatomic site of metastases according to primary (Berlit et al., with permission).

Size

The size of the metastases is almost never addressed in the data studies. Strang et al. tried to correlate size with their EEG-findings without reaching any conclusion, but noted that the largest was 5x6. No farther statistical data were provided. Willis founds a number of solitary large-sized metastases with diameters up to 10cm.
According to Nieder et al., about half of the metastases are smaller than 2 cm. Only 1% are larger than 5 cm (table 5.10).

Table 5.10 - Cerebral Metastases
Size and Histology
Data of Nieder et al., 1995

Size	Primary NSBC N=202	SCBC N=65	Breast N=80
<1.0 cm	26.2%	30.8%	25.0%
1.0-2.0 cm	35.6	26.2	36.3
2.1-3.0 cm	26.2	32.3	23.8
3.1-4.0 cm	6.9	6.2	11.3
4.1-5.0 cm	1.0	4.6	2.5
>5.0 cm	1.0	--	1.3

NSBC: Non-small Bronchial cancer; SCBC: small cell bronchial cancer

Left/Right

Some studies have mentioned a predominance on the right side, but large series have not. Studies dealing with primary, gender and age are lacking.

Number

Multiplicity is most common, but according to Gonzalez et al. only 5% have more than 5 lesions.
Reliable data are difficult to find in the literature. We quote here those from Nussbaum et al. on 729 patients, (table 5.11). They are similar to the data from Graf et al. not shown here.

Table 5. 11- Cerebral Metastases
Proportion of single vs.multiple metastases (N=729)
Data of Nussbaum et al., 1996

Primary	N	Single	Multiple
Bronchus non-small	178	50%	50%
Bronchus small cell	110	43	56
Breast carcinoma	121	49	51
Melanoma	80	49	51
Kidney	45	56	44
Gastrointestinal	45	67	33
Uterine-vulva	38	53	47
Unknown	33	70	30
Ovaries	14	57	43
Urinary bladder	14	64	36
Prostate	11	82	18
Testis	11	55	45
Various others	29	65	35
All patients	729	53	47

It is obvious that there is almost no difference between the different primaries, except for prostate which has a high proportion of single cerebral metastases.

As half of the patients have only 1 metastasis, the possibility should not be excluded that the numerical distribution of the metastases follows Bradford's law. Data are however lacking.

As we will discuss later, the adveent of better imaging methods has dramatically reduced the number of patients with single metastases. The data provided by Swift et al. from a series of 728 radiation-treated patients shows this clearly (table 5.13).

Influence of Gender

With the exception of the typical cancers for each gender, the incidence according to gender is almost not documented.
An series dating back to 1973 by Van Parijs et al. did make the distinction, though only in respect of the respective incidence of each primary within the gender group (table 5.14).

Table 5.12 - Cerebral Metastases
Comparison of Site distribution between single and multiple metastases (Data of Egawa et al.)

	Solitary				Multiple(')			
	Bronchus N=50	Breast N=12	Other N=31	Total N=93	Bronchus N=173	Breast N=28	Other N=74	Total N=275
Frontal	4.0%	--	12.9%	6.5%	21.4%	17.9%	30.0%	21.5%
Temporal	16.0	8.3	3.2	10.8	13.9	7.1	10.8	12.4
Parietal	24.0	25.0	22.6	13.7	21.4	25.0	24.3	22.5
Occipital	28.0	--	25.8	23.7	24.9	28.6	20.2	24.0
Other(")	6.0	32.2	9.7	10.8	11.2	7.1	9.6	9.5
Cerebellum	20.0	25.0	3.2	15.1	6.4	7.1	8.1	6.9
brain stem	-- 8.3	16.1	6.5	1.1	3.6	4.0	2.2	
Unknown	2.0	--	6.5	3.2	1.1	3.6	--	1.1

(') Probably only the prominent site considered, as the total number equals 100%.
(") including fronto-, temporo- and occipitoparietal site

Table 5.13 - Metastases to the Brain
Number of metastases as detected on CT (N=728)
Data of Swift et al.1993

Number of lesions			
1	44%	4	8%
2	25%	>4	21%
3	10%	5-10	10%
1-3	79%	>11	3%

In the large autopsy series by Pickren et al. (table 5.4), there was no difference in the incidence rate according to gender: 8.8% in men vs. 8.7% in women. It was observed only that testicular tumors had a higher metastatic rate (20.7%) than ovarian tumors (1.9%). In the small number of penis cancers, 12.5% had brain metastases while only 3.5% of the patients with tumors of the female genitalia had brain metastases.

Table 5. 14 - Metastases to the Brain
Difference according to gender (number of type1 meta)
Data of VanParijs et al. (N=312)

	Women	Men
Bronchus	16(8)	178(105)
Breast	36(5)	1 (0)
Intestine	7(4)	13 (1)
Kidney	1(0)	10 (4)
Adrenal	0	3 (2)
Uterus-Ovary	5(1)	--
Prostate	--	3 (0)
Testis	--	4 (0)
Urin.Bladder	0	1 (0)
Unknown	4(4)	18(18)

More pertinent data on gender distribution can be extracted from a table provided by Johnston et al. based on the data of Takakura et al. We modified the table by eliminating the specific female cancers, so that comparative data could be obtained (table 5.15).
It will be seen that if breast cancer is not taken in account, the relative distribution of the different primaries is no different in either gender. There is clearly a higher proportion of melanomas and even of the various other primaries. When breast cancer is taken in account, they make more than one half of the brain metastases in women

Table 5.15 - Metastases to the Brain
Autopsy Data according toGender
from Johnson et al., based on Takakura et al.

	Men (N=452)	Women (N=218)
Bronchus	55.5%	45.0%
Gastrointestinal	10.2	13.7
Urinary Tract	7.3	8.7
Melanoma	5.3	10.5
Prostate	8.2	--
Head and Neck	3.8	5.5
Sarcomas	1.3	6.4
Liver,Bile, Pancreas	3.1	3.7
Thyroid	1.5	3.6
Others	2.4	2.7
Breast		272/511 = 53.2%
Female Genitalia		21/511 = 4.1%

Influence of Histology

This is discussed separately for each primary. Adenocarcinomas have globally a higher incidence rate (table 5.16). Brain metastases from sarcomas are rare. Before the eighties, virtually single cases appeared in the literature. Since oncologists are applying more aggressive treatment and obtained better survivals in soft and bone sarcomas, a larger number of patients with brain metastases have been observed.

Table 5.16- Metastases to the Brain
Incidence rate for Adenocarcinoma
Autopsy data of Pickren et al.

Adenocarcinoma of the	
Bronchus	33%
Breast	17%
Kidney / ureter	13%
Uterus	6%
Pancreas	9%
Colon	5%
Stomach	4%
Rectum	3%

Up to 1979, there had been 25 cases in the literature (review by Ho) and in 1985, Sarno et al. were able to find 55 cases in the american literature, 34 from soft tissue and 21 from osseous tumors. These two reviews do not correlate, so that conclusions are somewhat difficult to draw. In another review, Lewis collected 94 cases in 1988, apparently also somewhat different (table 5.17).

Table 5.17 - Sarcomas metastatic to the Brain
Histology of Primary involved
Literature Review by Lewis 1988

Soft tissue			
Alveolar soft-part	15	Liposarcoma	6
Angiosarcoma	2	Mal. fibr hist	8
Cystosarcoma	2	Mix Mal. Mesench	1
Epithelioid sarcoma	1	Rhabdomyos	8
Fibrosarcoma	14	Synovial sarc	1
Leiomyosarcoma	11	Other unspec .	4
Osseous			
Chondrosarcoma	4	Osteosarcoma	7
Ewing sarcoma	9	Giant cell sarcoma	1

In pathologically verified cases, the interval between diagnosis of the primary and the occurrence of the brain metastases, was between 1 and 13 months for soft part sarcomas, with the exception of alveolar soft-part sarcoma which had intervals of 24 to 180 months. For osteosarcoma and Ewing, the interval was 9-24 months.
Nevertheless, in the literature they found 4 cases of type 1 metastases, and added two where the brain metastases revealed a peripheral sarcoma (table 5.18).

Table 5.18 - Type 1- Sarcoma Brain Metastases
Literature collected by Lewis

M25	Thigh	Alveolar soft-part sarcoma
M25	Heart	Fibrosarcoma
F60	Retroperitoneum	Fibrosarcoma
M84	Chest wall	Leiomyosarcoma
M24	Stomach	Leiomyosarcoma
M79	Lung (?)	Rhabdomyosarcoma

Table 5.19 - Sarcoma metastases to the Brain
Location within the Brain
Data from four surgical series (')

Site	Sarcoma Type Soft tissue	Osseous
Frontal	16	12
Parietal	11	2
Temporal	3	1
Occipital	2	4
Parietooccipital	3	2
Parietofrontal	5	2
Cerebellum	1	0
Multiple	8	0

(')Bindal et al. 21 pat., 24 metast., Wronski et al. 25 patients; Salvati et al. 15 patients, Ogose et al. 20 patients.

The brain site involved with the sarcoma metastases would appear to be relatively specific, as the majority seem to be located within the frontal region. We took the data from three recent surgical series together in table 5.19.

Influence the patient's Age

Only a few authors have related age to the frequency of cerebral metastases. All noticed a decrease with age. It has been asserted that the frequency is lower at old age as either time to establish metastases is shorter and/or the brain is not always examined at autopsy (Aronson et al.). They could demonstrate the decrease according to increasing age for different primaries in both genders. Fig.5.7 shows the overall age curve.
A large autopsy series of 10916 oncology patients also disclosed also a declining trend of the incidence of metastases within the age-group. This is at variance with the increasing incidence when age group is considered for the patients with brain metastases.

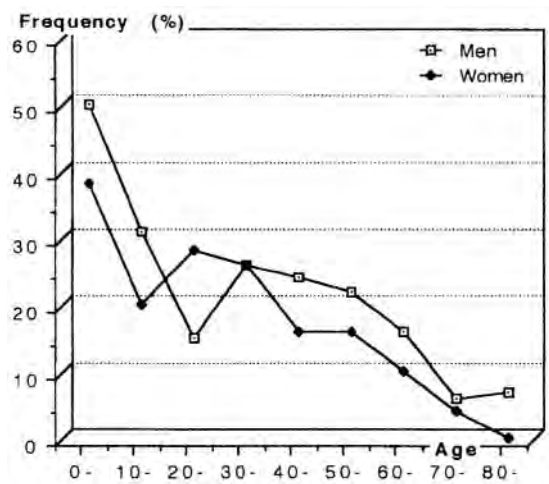

Fig.5.7 - Relationship of age of the patient to the incidence of metastases (Drawn from data of Aronson et al.)

Brain Metastases in Children

The incidence of brain metastases in children is poorly documented. A multicenter study of the Lyon Hospitals in France found that 12 patients had developed brain metastases at some time during their evolution in 486 patients or only 2.5%. Other series reviewed by the authors, reported an incidence of 6 to 12%. The type of primary most involved is apparently osteosarcoma or Ewing's sarcoma, but the numbers are not significant.
According to a study by Graus et al. of the files of the Memorial Hospital in N.Y., the incidence of brain metastases was highest in germ cell tumors (50%), and approximately 14% in osteogenic sarcoma, rhabdomyosarcoma and Ewing's sarcoma. They found an incidence of 12.9% (18 of 139 patients).

Neurological symptoms led to the diagnosis in 80% of the patients, while the other 20% were found only at autopsy. Increased internal pressure (50%), hemiparesis (36%) and altered mental status were the main

first symptoms, together with seizures with 36%, which is certainly more than in adults. They are even more frequent in patients younger than 15 years (50%). Solitary metastases were observed in 7 patients. Symptoms are much more abrupt at onset than in adults. Abrupt symptomatology occurred in 20%, mostly due to hemorrhagic metastases.

Interval Occurrence

As we will discuss later, quite a number of brain metastases are first signs of a primary malignant tumor. In the other patients they occur later. There is apparently a difference in time interval according to the primary involved (table 5.20).

Table 5.20 - Cerebral Metastases
Time Interval of appearance of metastases
Data of Kishi et al.

Primary	N	First year	Later
Bronchus	48	34 69%	14 29%
Breast	12	3 25%	9 75%
GIT	7	2 28%	5 72%
Uterus	5	0 --	5 (100%)
Other	14	1 7%	13 (93%)
All patients	86	40	46

The median interval between diagnosis and brain metastases in children is given on table 5.21, and is compared with the median interval for lung metastases. The median interval for lung and brain metastases was 10 months.

Table 5.21 - Brain Metastases in Children
Interval from diagnosis to occurrence (N=25)
Data of Graus et al. 1983

Tumor Type	Time to Lung Metast.	Time to Brain Metast.
Osteogenic Sarc.	8 mo (5-22)	22 (10 - 36)
Germ Cell Tumor	1 mo (0-12	13 (0 - 39)
Rhabdomyosarc	1 mo (0-144)	8.5 (3 - 44)
Other	1 mo (0 - 26)	20 (10-60)

Nussbaum's large series is in table 5.22, and it gives the mean duration of diagnostic interval for the different primaries.

Table 5.22 - Cerebral Metastases
Mean interval from diagnosis to metastases (N=729)
Data of Nussbaum et al.

(in ascending order, months)

Bronchus	3	Uterine-vulvar	23
Bronchus(small cell)	6	Ovary	23
Gastrointestinal	14	Renal cell	28
Urinary Bladder	15	Melanoma	31
Testicular	15	Breast	40
Prostate	22	Various	16
Total Cohort		mean: 12 months	

Macroscopic Aspects.

Apart from the location or multiplicity, several pathological types can be discerned. They correlate more or less with the type of primary (table 5.23) (Peretti-Viton et al.).

Table 5.23 - Cerebral Metastases
Pathology types (Modified from Peretti-Viton et al.)

Type	Primary
Nodular	Breast, kidney, rectum, uterus
Infiltrative	Bronchus
Cystic	Digestive tract (adenocarcinoma)
Hemorrhagic	Melanoma, choriocarcinoma, retinoblastoma, kidney, thyroid
Abcess-like	Bronchus
Hypervascular	Bronchus, breast, kidney, thyroid, melanoma
Pseudo meningiomatous	Breast (with infiltration of dura)
Calcified	Kidney,...

Several exceptional situations may be encountered, each with a particular clinical presentation.

Miliary metastases

This is a very rarely reported situation, in spite of the fact that the majority of patients have multiple metastases. Madow et al. coined the term 'carcinomatous encephalitis' to describe a diffuse perivascular distribution of tumor cells producing innumerable tiny tumor nodules. The most frequent primary involved is bronchial carcinoma.

Up to 1997, there had been about 10 cases of miliary metastases reported, and these were described as diffuse and innumerable. Three concerned an adenocarcinoma of the bronchus and one from an acinar cell carcinoma of the pancreas (Bhushan). All the metastatic lesions were calcified. The spread include both hemispheres, but also brain stem and cerebellum. Symptomatology can be very misleading as there is almost no mass effect and no tissue-glial reaction, probably because of an altered local immune brain reaction. Most cases were discovered at staging procedures. At the imaging procedures, contrast enhancement is poor or absent due to their minute volume. They are best visualized at T2-MRI (Nemzek et al.).

Under the description 'carcinomatous encephalitis', Olsen et al. reported on a woman presenting in semicomatous habitus, with at CT multiple small nodules in gray and white matter and basal ganglia. Histology revealed papillary adenocarcinoma, but the primary was not searched for.

We question the identity with leptomeningeal metastases. The description of the case reports in the article by Madow et al. are indeed quite similar, as in several patients 'the leptomeninges were moderately thickened with a fibrous proliferation and diffuse cellular infiltration…'.

Subdural metastases and hematoma

Metastases to the dura mater are relatively rare. They have also been described as pachymeningitis. Subdural fluid collections due to metastatic neoplastic diseases of the dura mater are rarer. The entity of dural metastases has been discussed only sporadically in the literature; the complicating subdural hemorrhage-hematoma receiving much more attention.

The association of dural metastatic disease with a subdural hematoma is rare. It has a frequency between 0.4 to 5% in autopsy-series (review by MacKenzie et al.). In a series of 2,508 oncologic patients, 437 had metastases to the nervous system, with 38% involving the meninges and only two cases associated with subdural hematoma. Vonofakos et al. collected 34 cases in the literature.

Bergman et al. reported 9 cases from the literature, to which they added one. The clinical picture can be slowly progressive (chronic) or acute. Dural invasion is usually accompanied by skull deposits, but develops after widespread metastases. Headache, lethargy and personality changes are common in these cases, and coma develops in acute situations complicated by hemorrhages. Diagnosis is usually made at CT, although rather insensitive for meningeal neoplasms.

The involved primaries are shown in table 5.24. Another survey in 1990 by MacKenzie et al. is added. The review by Vonofakos et al. also mentions 9 cancers of the stomach, 6 of the prostate, 3 of the pancreas and one biliary, esophageal, melanoma and 5 sarcomas.

A variant(?) of this situation is a solitary brain metastasis with dural extension.

Table 5. 24 - Cerebral Metastases
Subdural metastatic hematomas
Literature reviews

	Bergman	MacKenzie
Prostate	3	6
Bronchus	2	1
Testis	1	1
Liver	1	1
Rectum	1	--
Testis (seminoma)	1	1
Stomach	1	3
Other	--	4(')

(') Esophagus, penis, cervix, endometrium, unknown each 1 case.

In 1983, Furui et al. reported 4 cases, of which 3 stomachal cancers and 1 rhabdomyosarcoma. They found only 5 cases in the literature, of which 1 from a cervix uteri cancer. The number of reports on metastatic cancers as a cause of subdural hematoma is small. Reporting on two cases from prostate cancers, Bucci et al. in 1986 were able to find 27 reports without giving further details. Villette et al. reporting a case of bronchial cancers in 1987, collected 23 cases from different sources. They state that 4 cases were from a stomach cancer and 3 from prostate cancer.

The mechanism of subdural hematoma formation could be based on two mechanisms: bleeding of a metastatic tumor within the subdural space or invasion of the subdural vessels. Another hypothesis is obstruction of venous vessels in the external layer of the dura by tumor cells leading to the dilatation of capillaries and disturbances of the blood circulation with ruptures of the capillaries. Direct in-volvement of the dura is also possible with destruction of the vascular wall.

According to Rumana et al., patients with dural extension are different from the above described group and may be considered to have a poorer prognosis.They reported on 22 neurosurgically treated patients, from a group of 425 patients undergoing craniotomy for metastatic disease. The metastases were most frequently attached to the dura along the convexities, fewer at the falx and tentorium. Compared with other patients with brain metastases, there were slightly more female patients, fewer renal primaries (table 5.25) and more seizure, visual disturbances and speech problems. We have added the review by Ambiavagar et al., which shows totally different primaries.

Table 5. 25 - Cerebral Metastases
Patients presenting with dural extensions
Involved primaries in 2 literature series

Rumana et al.		Ambiavagar et al.	
Breast	5 cases	Stomach	2cases
Bronchus	6 cases	Penis	1
(4 adenocarc, 2 epiderm)		Breast	1
Kidney	2 cases	Prostate	2
Melanoma	2 cases	Bronchus	1
Adenocarcinoma	6 cases	Pancreas	2
(1 unknown)		Ewing sarc	1
Germ cell	1 case	Cervix	1
(site not given)		Unknown	1

A small series was recently reported of 18 patients. While in twelve the primary was not found, melanoma was found in 8 (Schrader et al.). Numerous mechanisms must be involved when one reviews the reported cases. A common frequent one is a metastasis on the cortical surface undergoing abrupt hemorrhage. Spread into the diploe, either through the arterial circulation or the meningeal vessels or the venous plexus of Batson, as seen in prostatic carcinoma, is another mechanism. This is in fact a bone metastasis with secundary intra-calvarial problems.

The formation of a subdural neomembrane distinct from a membrane associated with a subdural hematoma, has been described leading to a hemorrhage within abnormal areolar layer of the dura. On the other hand, metastatic spread could also occur in a preexistent chronic subdural hematoma. However veins and venules can also be infiltrated with tumor cells resulting in dilatation and rupture of capillaries with subdural hemorrhage.

Two radiological forms can be distinguished

(Khalfallah et al.). The most frequent is probably the hemorrhage form presenting as a chronic subdural hematoma. In a review by Turner et al., the majority were from an unknown primary. The other type or tumoral form should be rarer, although differentiating between both is not always easy. It can present either as limited, hardly visible dural thickening or a larger meningeal plaque simulating a meningioma. The MRI is very important as stressed by Khalfallah et al., in order to visualize the tumoral part of the process and the dural thickening at the periphery of the tumoral infiltrate.

Autopsy studies have reported metastases involving the dura in 10% of carcinoma and sarcomas, breast carcinomas scoring higher than the mean, probably because of their affinity for bone.

Differential diagnosis with the much more common disseminated intravascular coagulation should be done.

Cystic Metastases

Cystic, and possibly necrotic metastases have been described repeatedly. They are, in fact, common.

Calcified Metastases

Metastatic cerebral metastases rarely contain calcium. Occasionally calcification shows up on the images. The few reports concern almost only adenocarcinomas of various origins or sarcomas.

In view of the long period necessary to develop calcium deposits, it appears more frequently in benign or slow-growing neoplasms. This could be a feature of long-standing or slow-growing metastases.

It is found in 1.1% of the surgical specimens and in 6% at autopsy (Tashiro et al.). Reviewing the literature up to 1990, Tashiro could find only 17 cases. Those prior to 1979 were found at plain radiographs, while the later ones were detected at CT (table 5.26). The calcification can be very vague but in other cases very pronounced. Most have a heterogenous hyperdense structure with high-density nodules.

Table 5.26 - Cerebral metastases
Reported cases of calcified metastases
Literature review by Tashiro et al. (1990)

Bronchus adenocarcinoma	7cases
Breast adenocarcinoma	1case
GIT adenocarcinoma	4cases
Unknown primary adenocarc.	1case
Sarcoma of the bone	2cases
Mediastinal sarcoma	1case
Sarcoma unknown site	1case

Nearly half of these were from a bronchial adenocarcinoma and there were 4 sarcoma, of which 2 osteosarcoma, well known for their calcifying metastases. This has probably been underreported.

Reviewing the osteosarcoma literature, Kincaid could retrieve only 13 cases of brain metastases. Some were described with calcification. They added one case.

The calcification was described as punctate, curvilinear or amorphous in seven cases by Anand et al. (2 colonic, 3 bronchial, two breast cancer and one from esophageal cancer).

A more recent review by Hwang et al. found also cases from uterine, ovarian, pancreatic and some epidermoid carcinomas.

Differential diagnosis with calcifying intracranial epidermoid carcinoma is mandatory but not difficult. This tumor occurs near or at the midline, especially in the posterior fossa, usually has a cystic appearance and tends to disseminate further similar to meningeal carcinomatosis. This tumor also infiltrates the brain parenchyma.

Hemorrhagic Metastases

This type of metastasis as seen at imaging, and is associated with several primary neoplasms. Malignant melanoma, but also bronchial, renal and the 'placentar' choriocarcinomas, are the most frequent. The parallelism with the high vascularity of the primary is obvious. Melanomas and choriocarcinoma can produce large hematomas within small tumor deposits. The presence of choriocarcinoma elements could explain the occurrence of this type of metastases in teratomas, but these elements are almost never present. Metastases of teratomas can, however, be more aggressive than the primary.

The incidence is 1 to 3% in primary gliomas, and 3 to 14% in metastases (Atlas et al.). The pathogenesis is probably multi-factorial. A high grade of malignancy, extensive and abnormal vascularity, rapid tumor growth and vascular invasion are the possible factors predisposing to this situation.

They present with a particular pattern at MRI. Zones of hyperintensity, either central or in the periphery correlates with the blood extravasation. This has been fully described by Atlas et al. (table 5.27).

Table 5.27 - Hemorrhagic Cerebral Metastases
Specific MRI characteristics (Modified from Atlas et al.)

1. An overall signal intensity pattern complexity or heterogeneity
2. Presence of focal abnormal tissue not corresponding to any signal intensity pattern described for hemorrhage
3. Delayed temporal evolution of hemoglobin states inferred from changing signal intensity patterns
4. An absent, diminished or irregular rim of marked hypo-intensity on long TR/ long TE images, indicating hemosiderin
5. Pronounce and persistent edema
6. A location atypical for aneurysm or hypertensive hemorrhage

Neoplastic Aneurysms

Intracranial neoplastic aneurysm due to metastatic

tumor embolization of the cerebral arteries is rarely reported. It is a well known complication of cardiac myxoma. Up to 1982 it was mainly reported in choriocarcinoma (5 cases) one in a bronchogenic carcinoma (Ho) and one with an unknown primary.
The clinical picture correlates with an intracranial (subarachnoidal) hemorrhage or chronic progressive deterioration with signs of intracranial hypertension.
The literature states that spontaneous intracranial hemorrhages occur 1 to 10% of the patients with cerebral or subarachnoidal hemorrhage. It should be more common in metastatic than in primary brain tumors, up to 14% (Mandybur et al.). One probable reason is the defective vascular structure of the metastases, but also the invasiveness of some within the brain tissue at the surface with segmental destruction of the vessel wall after formation of an aneurysm.

Symptomatology of Brain Metastases

Most, at least 80%, of the cerebral metastases are symptomatic. More than two thirds of the patients with metastases have neurologic symptoms during their evolution.
The clinical presentation is no different to that for secondary or primary brain tumors, or any other mass lesion.
Any patient with a known tumor presenting with cerebral or neurologic symptoms must be examined to see why this new symptoms have developed.
The symptoms can be divided into those caused by the mass effect and those due to their location within the brain.
The presence of mass causes headache, papilledema, visual blurring and nausea / vomitus.
Headache is a common symptom, and frequently the first symptom followed within days or weeks by other symptoms. Early morning headache is present in only 40%. Headache is more common with multiple lesions and with secondaries in the posterior fossa.
The headache is usually mild, diffuse or bifrontal without any localizing value. Some have reported that any focal headache may be localized to the site of the lesion in up to 70% of the patients. Apart from intracranial pressure, it can be caused by the traction exerted upon pain-sensitive structures such as the venous sinuses or the dura mater at the base of the skull.
When undiagnosed and untreated the headache will become more pronounced, especially in postural changes or in any straining.
Nausea and vomitus, especially in the morning is also a common symptom, in the beginning difficult to distinguish from other causes such as metabolic dis-

Table 5.28 - Cerebral Metastases
Focal Signs

Site	Symptom or Sign
Frontal	Behavior disturbances
Centro-Parietal	Apraxia, astereognosis
Temporal	Convulsions, focal epilepsia, hearing problems
Occipital	Vision problems
Broca	Aphasia.

Table 5.29 - Metastases to the Brain - Symptoms and signs at presentation (literature series)

Author	Order 1968 N=108	Nisce 1971 N=560	Brady 1974 N=167	Berry 1974 N=124	Posner 1974 N=164	Zimm 1981 N=191	Sauer 1986 N=252	Nussbaum 1996 N=729
Symptom								
Motoric	65%	75%	37%	40%	66	34%	44%	16%
Intellect impairment	47	--	17	41	77	29	17	24
Headache	42	33	35	42	53	38	46	24
Sign								
Convulsions	26	18	13	25	15	--	11	16
Ataxia	--	--	--	--	20	11	--	--
Aphasia(')	--	21	--	--	20	6	13	5
Sensory Problems	16	28	--	10	27	2	--	2
Cerebellar	17	--	--	24	--	--	--	--
Loss of consciousness(")	8	41	--	--	--	25(°)	18	--
Papilledema	--	13	--	25	26	3	--	--
Cranial nerve	47	--	--	44	--	3	52	--
Visual problems	--	15	--	25	--	6	8	6
Diplopia	--	14	--	--	--	--	--	--
Dizziness, Vertigo	--	8	16	--	--	11	20	--
Nausea Vomitus	--	17	--	19	--	--	36	5
Gait disturbance	--	--	--	--	--	--	--	9
None	--	--	--	--	--	--	--	10
% Bronchial cancer	65%	25%	70%	30%	--	64%	37%	39%
% Breast cancer	12%	39%	11%	17%	--	14%	25%	17%

(') sometimes labeled as speech problems or dysarthria.
(") includes sometimes disorientation, lethargy, coma.
(°) of which 14% lethargy, 8% stupor.

turbances in the patient.
Papilledema is a symptom occurring at a later stage and is due to increased internal pressure. Serious visual blurring is the rule. It appears to be less common in the most recent series, due to earlier diagnosis of the metastases.

Other symptoms must be correlated with the site of the metastases. It is very strange that the literature never relates it with site. A correlation can be inferred from the data reported for primary tumors (table 5.28).
Seizures, focal or general, are present in 10-20% of the patients. It can occur in temporal-lobe metastases, but also because of the intracranial pressure. It is more common with multiple metastases. The incidence of focal seizures increases with the further evolution, in about half of the patients.

Of 411 patients presenting with seizures, 50 or 12% were due to a cerebral tumoral process, of which only 8 due to metastases or 16% of the tumor patients or 1.9% of all patients (Neundörfer et al). It concerned 3 bronchial cancers, 2 breast, 1 melanoma, 1 colonic and one from the urinary bladder. Except for one the metastasis was located in the parietotemporal region, the one in the occipital. A possible cause for the rare occurrence of seizures in metastases (and in primaries) could be the rapid destruction of the motoric cells.

At least one third of the patients suffer from focal symptoms such as hemiplegia. As is well-known, any hemi-syndrome points to the motor zone of the contralateral hemisphere, either invaded by a metastasis or to edema caused by neighbouring site.

Mental function is most frequently disturbed in frontal lesions, and will appear under various clinical presentations. Problems with memory, mood and personality is reported by about one third of the patients, but when further tested, present in up to 75%.

Acute symptoms at presentation are rare, but can be due to hemorrhages of the metastases, as is common with choriocarcinoma and melanoma. Massive hemorrhages can develop within a deep intracerebral metastatic tumor, shatter it, swell and result in edema and necrosis in peritumoral tissue. Moreover, they can occur in any location in the hemisphere, resulting in a large variation of symptomatology within the ictal or ruptured aneurysm presentation. One of the possible complications is chronic subdural hematoma, discussed elsewhere.

A series of 15 patients with massive cerebral hemo-rrhage was reported by Mandybur. It concerned mainly bronchial cancers(8), three choriocarcinomas, and one from the larynx, the kidney, testicle and one unfound.. Except the three choriocarcinomas and two bronchial cancers all were men. In ten patients, the primary was unknown before the 'stroke', even the choriocarcinomas.
Gait symptoms are probably more frequent in cerebellar metastases and speech problems are due to the involvement of the zone of Broca.

A very rarely reported clinical situation due to metastasis is hemiballism. This is characterized by violent choreiform movements of a large amplitude limited to one side of the body. Coordination may be normal, but excitement and emotional disturbances result in wild trashing of the affected arm and leg (French's index). It is the overt clinical manifestation of disinhibited thalamic outflow when tonic sub-thalamic activity is interrupted. It has been reported secondary to metastasis from cancer of the breast, the gallbladder and bronchus. A recent case was reported from cervical cancer with a localization within the cerebral peduncle extending into the inferior aspect of the basal ganglia complex (Ziainia et al.). A literature review of the metastatic cases is shown in table 5.30.

Table 5.30 - Metastases to the Brain
Primary involved in Hemiballism
Modified from Glass et al.

Author-Year	Pat.	Primary	Pathology(')
Bremme 1919	F40	Breast	Subthalamic Caps - Pons
Pette 1922	F68	Breast	Subthalamic
Bonhoeffer 1930	F52	Breast	Thalamus
Kelman 1945	M56	Bronchus Ad	Subthalamic
Lemmen 1957	M59	Gallbladder	Thalamus
Thompson 1960	M80	Bronchus SC	Subthalamic
Lewis 1968	M74	Bronchus Ep	Thalamus Cerebellum
Glass 1982	M78	Bronchus Ad	Subthalamic
Bronster 1983	F64	Bronchus Ad	Subthalamic
Ziainia 1999	F38	Cervix Uteri	Basal Ggl.

(') abridged.

Transient global amnesia associated with a single hemispheral metastasis from a bladder carcinoma (type-3) has been reported by Findler et al. Several cases with primary tumors have been reported, but none with a metastasis. The localization in the brain was always thalamic.
The symptomatology of brain metastases as reported in different literature series is brought together in table 5.29. As could be expected there is a large variation in the data due to the precision and dedication of the first examiner, but the data are undoubtedly influenced by the type of patients presenting.
Most series show a majority of bronchial cancer patients, but it is difficult to distinguish the influence of the primary on the symptomatology pattern. Recent series differ from older series in their diagnostic modes.
Some symptoms are probably reported in various ways. Diplopia is probably reported as a visual complaint, while gait disturbance is certainly cerebellar in origin.

Symptomatology of type 1 Metastases

The data from the series of VanParijs et al. provide some insight in the different symptomatology between

type 1-(revealing) metastases and those occurring later in the evolution (table 5.31).

Table 5.31 - Cerebral Metastases.
Differences between revealing and follow-up metastases
Data of VanParijs et al.

Symptom-Sign	type 1 Women N=22	Men N=131	Type2-3-metastases Women N=55	Men N=104
Headache	11	50	20	32
Hemiplegia	7	40	20	37
Epilepsia	1	14	6	16
Mental disturb.	1	12	5	4
Ataxia	1	5	0	5
Vertigo	1	6	2	4
Visual disturb.	0	2	2	4
Vomiting	0	2	2	4
Polydypsia	0	0	0	1
Whole group	22/77 28.6%	131/235 55%		

The data show that in 55% of the men the primary was unknown before presentation and in women 28%. To our knowledge, more recent data are not available in the literature.

Metastases in SPECIFIC LOCATIONS

A small number of patients have specific symptoms, due to the rare location of the metastases. Modern imaging capabilities has made individualization of these clinical situations possible.

Metastases to the Third Ventricle

This is very rarely reported. We found mention of four metastatic cases in a series of 262 tumors at that site. One revealed a colonic cancer, one was a renal cell cancer metastasis, one was a malignant melanoma and another from an unknown primary (Lejeune et al.).
Another case was reported as presenting with diabetes insipidus due to a small cell bronchial cancer with metastasis in the floor of the third ventricle (Noseda et al.).

Metastases to the Lateral Ventricles

This is a very rarely reported location. Jelinek et al. reported on 4 metastatic cases in a series comprising of 43 primary tumors of the region as including choroid plexus papilloma, meningioma and others. The authors did not report data on the primaries either how the diagnosis was made. CT and MRI are diagnostic of a malignant process, but histology was obtained with biopsy and at autopsy.
Other proved cases are rarely reported. An autopsy-proven case from bronchial oatcell cancer was reported on by Healy et al.
Metastasis to the periventricular brain tissue can obstruct the flow of CSF, causing typical obstructive hydrocephalus. Nguyen et al. have recently reported on seven cases with various primaries, including breast, ovary, rectum, bronchus and esophagus.
In contrast to primary intracranial tumors such as medulloblastoma, glioblastoma and ependymoma, metastatic dissemination of extra-neural tumors along the cerebrospinal fluid (CSF) pathway is extremily rare. Up to 1997, 9 cases should have been reported (table 5.32). At CT, best with contrast-enhancement, intraventricular seeding with hydrocephalus and diffuse ependymal metastases over the whole ventricular system is observed. Some also have leptomeningeal involvement. At pathology, extensive destruction of the periventricular and peri-aqueductal structures, as well as of the basal ganglia and medulla oblongata will be observed. The most probable pathway is hematogenous towards the choroid plexus. Some authors have considered it an important mode of spread to give rise to leptomeningeal carcinomatosis. The main clinical presen-tation is mental confusion, indifference and increasing, often fluctuating, drowsiness (Vannier et al.). Symptomatology might be masked while most patients also have many other metastases. Autopsy will confirm the diagnosis (Lee et al.).

Table 5.32 - Metastases to the Ventricular System
Case Reports and Primaries Involved
Modified from Lee et al.

Author	Patient	Primary	Metastatic site
Blinzinger 1966	??50	Bronchus	Left Parietal - ventricles
Blinzinger 1966	??47	Bronchus	Parietotemporal ventricles, Choroid
Hsu 1984	M69	OCBronch	Thalamus, hypothalamus, ventricle,stem
Vannier 1986	F55	OCBronch	Ventricle, Frontal, CPA
Vannier 1986	M55	OCBronch	Ventricle, choroid, LeptomeningealM
Vannier 1986	M50	OCBronch	Ventricles
Lee 1997	F58	OCBronch	Ventricle, cord, Medulla, LM
Lee 1997	M77	Bronchus	Ventricles, LM
Lee 1997	M53	Prostate	Ventricles, LM

(OC: oat cell-small cell cell; LM: leptomeningeal metastastases; CPA: cerebellopontine angle)

Parasellar and Cavernous Sinus Metastases

Metastatic lesions in this area probably start as bone metastases surrounding and lateral to the sella tursica. Rapidly invading tumors in any location near the sella may involve the supra- and parasellar space (Kattah et al.). Invasion of the cavernous sinus occurs along perineural and intraneural pathways. Various diseases may occur in this region. In the absence of histologic evidence, the diagnosis is difficult.
A few small series and some case reports have appeared. The largest, on 43 patients, was published

in 1970 by Thomas et al. It was part of a large series of 102 patients, containing 27 intracranial primaries and 32 with arterial aneurysms or aspecific inflammation.
A series of 16 patients was reported in 1985 by Post et al. On noteworthy feature is that 6 of them (35%) and 3 of the 4 of Bitoh were first presentation or type 1 metastases. All were unilateral. The primary involved is variable, but the highest number is from breast cancer. We have grouped the different series in table 5.33.
Four patients with a previously treated skin cancer (3 epidermoid and 1 melanoma) of the face, appearing several years after the first treatment, have been reported by Woodruff et al.

Symptomatology is characterized by the combination of headache, diplopia and dysfunction of the trigeminal nerve, sometimes with ophthalmoplegia, often referred to as the parasellar syndrome. The most striking feature was facial pain, often described as continuous, chronic, burning and intermittently stabbing. In the series by Katteah et al., ophthalmoplegia was the cardinal symptom.

Table 5.33 - Parasellar Metastases
Primaries involved
Literature Review by the author (°)

Primary			
Nasopharynx	4	Prostate	3
Salivary Gl. ectop.	2 (')	Intestinal (colon)	4
Breast cancer	15	Unknown	2
Bronchus	9	Kidney	2
Thyroid	2	Larynx	2

One case of uterus, testis, bone, melanoma , myeloma, liver, stomach (autopsy), liposarcoma of mesenterium
(') one must be considered as contiguous invasion.
(°) series and reports by Thomas et al.(1970), Post et al.(1985), Bitoh et al.(1985), Supler et al.(1992) Mills et al.(1981), Kattah et al. (1985) and Zahra (1986).

The process is slow, beginning with infiltration and expansion of one nerve, followed by the involvement of the adjacent cranial nerves. Evolution can take many months or even years.
Dysesthetic continuous pain in a division of the trigeminal nerve is very suggestive of intraneural infiltration by neoplastic cells (Unsold et al.).
A differential diagnosis between metastases and many other neurological diseases can be difficult.
Contrast-enhanced CT is the method of choice to visualize the parasellar metastases, but differentiation between other pathologies at that site is not easy.

Metastases to the Choroid Plexus

Metastases in the choroid plexus were reported be present in 19 cases of 737 (2.5%) autopsy cases according to one series (Schreiber et al., 1982). Seven other cases among 150 autopsies were described by Arendt et al.
A report in 1996 stated that only eight cases of single metastases in the choroid plexus had been published, to which Kohno et al. added three other cases. However, Chason reported an incidence of 7% and France had an incidence of 10% in the 150 autopsied cases with brain metastases. Almost all were male patients and the majority of the metastases were at the right lateral ventricle.

Table 5.34 - Single Metastases to the Choroid Plexus
Primaries involved

	Schreiber N=19	Kohno N=11(')	Raila(') N=15
Breast	2	1 (1F)	1
Bronchus	11	3 (3M)	4
GIT	2	--	--
Kidney	--	4 (3M,1F)	6
Female genitalia	1	--	--
Thyroid	1	--	--
Stomach	--	1 (1M)	--
Colon	--	1 (1M)	1
Unknown site	1	1 (1M)	--
Melanoma skin	--	--	1
Neuroblastoma	--	--	1
Lymphoma	--	--	1

(') Literature review

The primaries involved are shown in table 5.34. Metastatic tumors are frequently found around the foramen of Monro, in the body or in the trigone of the lateral ventricle (six cases).
One noteworthy aspect is that the kidney in spite of its low incidence of brain metastases, has 10 cases.
The diagnosis is mainly neuroradiologic, as specific symptoms are not described. Extensive peritumoral edema is recognized at T2-image, an important feature differentiating it from primary meningiomas.

Metastases to Cerebellopontine Angle

Metastases to the Cerebellopontine angle (CPA) have hardly received any attention in the literature. In a series of 1,354 CPA-tumors, Brackman et al. found only 3 metastatic tumors, but this was a series from an otology practice. The fact that from one institution, Yuh et al. were able to report on 14 patients, allows the conclusion that they are seriously underreported and probably hidden in the global series of brain metastases. We found 12 additional references to the subject, totalling 20 cases (table 5.35), including the 3 from Brackmann et al.

Cranial nerve dysfunction of the nerves of the internal auditory canal as rapid and total loss of hearing, generally the VIII (70%) but also III, IV, V,VI, VII and XI and XII can participate. Symptoms are fulminant and rapidly progressive, except in prostate cases, where the progression will be slow. In a few cases, invasion was found at imaging and was asymptomatic.
Needless to say that imaging, CT and/or MRI plays an important role in the delineation of the syndrome.

Yuh et al. report that the lesions at MRI were typically small iso-intense lesions and associated with extensive and rapidly progressive neurologic symptoms. The tumors had the same characteristics as acoustic neuromas, but the oncology history and other metastases should point to the diagnosis.

Table 5. 35 - Metastases to the Cerebellopontine Angle
Primary Tumors involved (N=31)
Literature Review by the author

Bronchus	8 cases	Prostate	2 cases
Breast	6	Oropharynx	2
Melanoma	2	Not specified	5

Kidney, Nasopharynx,, Colon, Unknown, Prostate Epidermoid NOS, Adenocarcinoma NOS, Lymphoma 1 case each

Metastases to Meckel's cave

Meckel's cave is located in the medial posterior portion of the middle cranial fossa. Within it lies the Gasserian ganglion of the nervus trigeminus and the subarachnoid trigeminal nerve. It can be described as a dural recess extending from the posterior fossa into the posteromedial portion of the middle cranial fossa (Kapila et al.).

While primary tumors such as meningiomas and neurinomas originating in Meckel's cave are well-known, metastatic tumors involving this site are rarely described.
Secondary tumors involving the cave can be divided into three groups. Firstly, they may be distant metastases from extracranial tumors. This is a rare occurrence, but a number of bronchial cancers have been reported. The first sign is usually a mononeuropathy of V or XII.
Subarachnoidal dissemination from the spinal cord or brain tumors or from metastatic processes within both may also result in deposits in the Meckel's cave. A few cases have been reported. The third group consists of a retrograde intracranial extension mainly from nasopharyngeal carcinomas, along the branches of the trigeminal nerve. This is discussed further in the chapter on this cancer and the perineural spread.

Symptomatology is related to irritation and/or deficit of the trigeminal nerve. Invasion of the ganglion causes severe continuous and unremitting facial pain, though involvement of the nerve roots rarely causes pain.
Tumors involving one or more of the peripheral branches cause atypical neuralgia, while malignant tumors arising from the skull, such as nasopharynx, present with facial dysesthesias, hypo-anesthesia and sometimes shooting pain.
There have only been a few reports of metastatic tumors at this location: three patients of whom one had breast cancer (Bullit). A number of nasopharyngeal and some sinusal carcinomas have been reported, but these cases it in fact wascaused by local extension through the skull base or along the cranial nerves.
One metastatic adenocarcinoma of unknown primary was reported by Tacconi et al.

Metastases to the Corpus Callosum

A man of 64 complained of recent headache, poor vision from the left eye, difficulties in expression, constant 'woozy' feeling and recent hoarseness. A CT revealed a large mass within the corpus callosum. A biopsy disclosed an adenocarcinoma, while on chest X-rays a left apical mass was also seen, also an adenocarcinoma (Watridge et al. 1981). Another case of metastasis in the corpus callosum was mentioned in 1953 by Meyer et al. in a autopsy-series of 216 patients with brain metastases. The primary was not cited.

Metastases to the Hypothalamus

This very rare metastatic site is hardly specifically addressed in the literature. Due to the important function of the hypothalamus, destructive lesions in this small anatomic structure can readily be suspected. Endocrine, vegetative and/or emotion dysfunction are the main clinical problem.
CT and MRI are the diagnostic method of choice, but differentiation from other destructive lesions is difficult, while the clinical information is important. The knowledge of previous tumor treatment and/or the presence of other metastases will lead to the diagnosis (Chakeres).

Metastases to Venous Sinus

Neoplastic involvement of the venous sinuses of the brain is uncommon. Mones reported on six cases in 1965, all confirmed at post-mortem examination. Five of them concerned children, two with neuroblastomas and three with Ewing'sarcoma. One adult had a cervix uteri carcinoma.
The clinical manifestations were engorged scalp veins or/and jugular foramen syndrome.
A woman presented with headache, temporal pain and malaise, subsequently followed by confusion and diplopia. Finally, at surgery, a thrombotic sagittal sinus was found with malignant cells. At autopsy, a gallbladder carcinoma was found (Smith et al.).

Involvement of Cranial Nerves

Specific reports on involvement of metastases within cranial nerves are very rare.
Isolated metastasis within the Gasserian ganglion has been reported from bronchial cancer, one oatcell (Delaney et al.) and an adenocarcinoma (Watridge et al.). 'Atypical facial pain' was the initial diagnosis. In

both patients the diagnosis was done at autopsy, when a solitary enlarged ganglion extensively infiltrated by carcinoma was found.
An isolated trigeminal nerve metastasis from breast cancer presented with unilateral facial pain and numbness. Surgery confirmed the isolated metastasis (Hirota et al.).
Caldas et al. reported on four patients with secondaries within the vestibulo-cochlear and facial nerves: one ependymoma of the cauda equina, one lymphoma, one bronchial (type not specified) and a type 1 metastases from a kidney cancer found at autopsy.
The pathway is subarachnoidal for the ependymoma, but certainly hematogenic for the other, although a progression along nerves within the spinal canal cannot be excluded.
Modern imaging methods can probably diagnose such metastasis earlier than was possible decades ago.

Metastases to the Pineal Gland

Metastases to the pineal gland have been reported in autopsy series. In recent decades, some cases have been detected in vivo even presenting as type 1 metastases.
In 737 systematically investigated oncology patients, Schreiber et al. found 13 patients with metastases in the pineal body or 1.7%. Eight of them were bronchial, 2 breast cancers and 1 case of GIT, gallbladder and malignant melanoma. Only three patients had a single pineal metastases. The Japanese Registry (Yanamoto et al.) found an incidence of 0.4% in 2280 autopsied cases with brain metastases.
Reviewing the literature in 1998, Schuster et al. found 35 cases (table 5.36). The majority of primaries were bronchial, mammary carcinomas and melanoma. This is at variance with a review by Yanamoto et al. in 1987, involving 43 cases with 21 bronchial cancers, 15 breast cancers, only 2 melanomas, 2 stomach and one gallbladder cancer.
In a series of 370 pineal tumors subjected to stereotactic biopsy, 10 patients or 2.7% were found to have metastatic tumors, but further data were not supplied (Regis et al.). In a series of 30 pineal tumors, one women was found to have a metastatic kidney tumor (Linggood et al.).

Table 5.36 - Metastases to the Pineal Body
Primaries Involved
Literature Review Schuster 1998

Bronchus	11	Pancreas	1
Breast cancer	9	Ovary	1
Melanoma	3	Stomach	1
Kidney	2	Frontal sinus tumor	1
Esophagus	2	Myeloma	1

A case has been reported presenting with revealing metastasis from a testicular germ cell tumor (Delahunt et al.). We are aware of 4 other type 1 presentations. Vaquero et al. reported on three patients, in whom subsequently a bronchial cancer, one metastatic melanoma and an undifferentiated carcinoma of unknown site were found. Another bronchial cancer was detected in a woman of 70 presenting with typical neurologic abnormalities (Keyaki et al.). Any tumor found in that region in any patient is more likely to be a primary pinealoma than a metastasis. The previous history of the malignancy will make metastasis more probable.

PECULIAR METASTASES

Mucin Embolisation

A situation encountered at autopsy is the occlusion of arteries of any size by mucin embols and resultant cerebral and systemic infarcts. The symptomatology in vivo is, as expected, very variable, ranging from widespread to variable localization. Most present with cerebrovascular symptoms simulating infarcts.
Diagnosis is, however, only possible at autopsy.
One of the first cases was reported by Robitaille in 1980. A man presented with a palet of neurologic symptoms, and fast progression and rapid death two weeks after admission. The brain at autopsy had multiple areas of ischemic necrosis with occlusion of several arteries and filled with a bland substance strongly positive for mucicarmin staining and very few neoplastic cells. This was the type 1 presentation of a bronchial adenocarcinoma unknown before death.
This is a clear but rare complication similar to neoplastic emboli but specific for mucin-producing adenocarcinomas. This pathology has also been described for pulmonary metastases.
A series of 6 patients was reported by Amico et al. englobing a colonic, a cecal cancer and 2 pancreatic and bronchial carcinomas each, all of the mucin producing-type adenocarcinoma. The clinical picture included stroke and encephalopathy.

Type 1 Metastases

The occurrence of brain metastases in a patient without known primary is a frequent situation encountered in oncology. Most of the patients (35 to 55%) are found with a bronchial carcinoma. The probable reason for this has been stated above. The problem is however hardly discussed in the literature, though many reports exist mainly concerning bronchial cancer. We refer to the relevant chapter (table 5.37).

The distribution of the primary found either on clinical, on imaging grounds or at autopsy is variable in the different series, except that bronchial cancer is the major involved one. (table 5.37). With the exception of bronchial primaries, the primaries are very variable. Case reports have also been reported. The presentation is apparently no different for type 1, type 2 or 3 metastases. Symptomatology is in table 5.38, taken from two series. The site of the metastases in the brain is rarely documented (table 5.39).

Table 5.37 - Type 1 - Cerebral Metastases
Site of Primary Involved
Literature data

Site	Chevalier 1985 N= 62	Eapen(') 1988 N=43	Salvati(") 1995 N=100
Bronchial	45.2%	14%	65%
Melanoma	8.1	5	10
Pancreas	8.1	--	--
Ovary	6.5	--	--
Thyroid	4.8	--	--
Breast	4.8	--	4
Digest.system	--	--	10
Kidney	--	--	5
Urogenital	--	--	3
Unknown AA	--	--	3

(') 74% remained occult (AA?)
(") only single metastases, AA: after autopsy.

Table 5. 38 - Type 1- Cerebral Metastases
Symptomatology at presentation
Literature data

Symptom	Eapen (1988) N=43	Nguyen (1998) N=39
Intracr.Hypertension	49%	Headache 48%
Motor deficit	47	25
A- Dysphasia	28	--
Seizures	26	20
Cranial nerve Deficit	19	--
Cerebellar	19	--
Behavior Modification	19	--
Sensory Deficit	12	2.5
Nausea / Vomitus	--	7.6
Other symptoms	--	23.0

Table 5. 39 - Type 1- Cerebral Metastases
Site of metastases within the brain
Literature data

	Salvati (1995) N=100 (')	Nguyen(1998) N= 39(")
Frontal lobe	25%	41%
Parietal lobe	24	48
Temporal	14	23
Occipital	11	13
Cerebellum	26	33
Thalamus-Brain stem	--	5

(') only single metastases; (")50% multiple

Even in the many series of patients undergoing surgery for solitary brain metastases, patient data concerning symptomatology and site of metastases are not reported.

Diagnosis - Imaging

The imaging of brain metastases has undergone tremendous evolution in the last decades. While in the sixties, brain scintigraphy was a serious step forward, the introduction of CT scan and subsequently of MR, has allowed an incomparably better visualization and even localisation within the brain of any even 'faint' metastases.

Table 5. 40 - Cerebral Metastases
Differential Diagnosis (Modified from Posner)

Primary Brain Tumor
- Meningioma, glioma

Cerebral hemorrhage
- Secundary trombocytopenia
- Metastasis (melanoma, choriocarcinoma)

Cerebrovascular
- Thrombotic
  - (disseminated intravascular coagulation)
- Embolic (nonbacterial thromb. endocarditis)
- Infarction

Infectious
- Abcess (pyogenic, fungal, other)
- (common in Hodgkin and NH-lymphoma)

Toxic Radiation necrosis

Metabolic
- Encephalopathy (organ failure, drugs)

Paraneoplastic syndromes
- Lambert Eaton, polyneuropathy

We will not discuss imaging problem in any depth, as there are many excellent reviews and textbooks on the subject.

There are no absolutely specific morphological criteria distinguishing individual types of brain metastases from the viewpoint of the primary. The most frequent shape is ring-like. Nodular metastases prevail in breast cancer and irregular ones are relatively rare. Peritumoral edema is much more present in supratentorial than in cerebellar metastases. Supratentorial metastases are usually smaller. According to Pechova et al., the ratio between enhancement and edema is constant in 70% of the metastases, demonstrating a common cause leading to these phenomena. Nodular metastases indicate a lesser tumor aggressivity. High malignancy is characterized by central necrosis and an ensuing ring shape focus, especially a thin layer covering the voluminous central necrosis (Pechova-Peterova et al.).

In a prospective study of 728 patients with radiation-treated brain metastases, the most frequently observed feature on CT was mass-effect (table 5.41).

Table 5. 41 - Cerebral Metastases
Pre-treatment CT characteristics (N=726)
Data of Swift et al.

Midline Shift	36%
Mass Effect	77%
Necrotic Center	52%
Massive Edema	19%
Hydrocephalus	8%

With MRI, the number of metastases detected has increased several-fold, especially with contrast-enhancement. Moreover, high-dose contrast T1W spin-echo with Gadolinium allows the detection of a higher number, but also of smaller metastases (Akesonet al.). Other characteristics of the metastatic images have been listed by Ferrozzi et al. (table 5.42).

Table 5.42 - Cerebral Metastases
Radiologic and Clinical Hints for Diagnosis
Modified from Ferrozzi et al.

Morphology	Structure	Other Sites	Primary
Supratentorial nodular	Annular homogenous	adrenal bone, liver thorac.node	Bronchus
Supratentoral nodular	Well or Ill defined, hemor	multiple	Melanoma
Supratentorial nodular -mening	Annular homogen	Bone, liver lung	Breast
Infratentorial nodular	Hemorrhagic	Bone, lung	Kidney

The radiological appearance of the cerebral metastases, together with knowledge of other metastatic sites in the patient can give clues for the diagnosis of the most probable primary, although this is of course not specific.

Ithas been argued that one can classify clinically the brain metastases according to the primaries involved into three groups (Kehrli):

1. Primaries with a high probablity of brain metastases. They are less frequently present in neurosurgical series, due to their fast evolution and infaust prognosis. The best examples are bronchial, particularly small cell. Another is testicular cancer as it is quite sensitive to the actual chemotherapy.
2. Primaries with lately occurring brain meta-stases, but mainly presenting as multiple nodules and associated with other metastases elsewhere. Breast and colonic cancers are representative for this group.
3. Primaries who rarely metastasize to the brain, rather late and slow in evolution, such as tumors of the uterus, thyroid, prostata and urinary bladder.

Differential Diagnosis

Although in most cases diagnosis is not difficult, other pathologies must be considered (table 5.40). The most frequent is another cerebral primary, and has been reported in a number of cases.

METASTASES to the CEREBELLUM

As table 5.7indicated, the incidence of cerebellar involvement is probably between 5 and 20% of all brain metastases. It seems much higher (around 20%) for bronchial and mammary cancers, but lower for abdo-minal and pelvic tumors.

Specific reports concerning these metastases are rare. We are aware of only two, one in 1987 by Fadul et al. and one in 1996 by Ampil et al. 1995. Of 367 patients known as having brain metastases, 45 individuals had cerebellar metastases, or 12.3% (Ampil et al.).

Most of the cerebellar metastases were located in one hemisphere and were single. 12% of the lesions were in the vermis. Three patients had multiple lesions.

The primaries involved are in table 5.43. As the series by Fadul concerns a Veteran Administration Hospital, breast cancer is underreported. The majority concerned bronchial tumors, up to 66% in the series by Fadul et al. and 75% in the series by Ampil et al. who gave no more details. Other data are however lacking.

Table 5.43 - Metastases to the Cerebellum
Primary Tumor involved (series of Fadul et al. 1987)

Bronchus	39/59 or 66%
Breast	7 or 12%
Melanoma	6
Colon	4
Uterus (NOS)	1
Prostate	1
Sarcoma	1

There have been case reports of a carcinoid, a prolactinoma, an urinary bladder and one uterine cervix carcinoma.

The median time interval between diagnosis of the primary and of the metastases was 15.5 months, but in 31% they were the first sign (type 1 metastases) of an unknown tumor (Fadul et al.). In one case of melanoma, the cerebellar metastases appeared 9 years after diagnosis of the primary.

In half of the patients discussed by Ampil et al., there were no other metastases (solitary metastases), but more comparative data were not given.

Symptomatology is relatively characteristic and may even dominate when multiple other metastases are present. Disturbance of coordination, gait and movements are well known symptoms of involvement of the cerebellum. The presenting signs in both cited series are in table 5.44.

The symptomatology in patients with single cerebellar metastases will be more specific as it will be 'less diluted' by the presence of other metastases. One interesting detail in the report by Fadul et al. is that 12% of the patients had only 1 symptom (table 5.43). The development of obstructive hydrocephalus is a possible complication, and is due to the proximity of the cerebellum to the fourth ventricle and the cerebrospinal liquid circulation. Some cite a frequency of 24% but Ampil et al. cite only 4%.

A series of 17 patients with a solitary cerebellar metastasis, 3% of all patients with intracranial metastases, was reported by Weisberg. The primary was a bronchial cancer in 16 and one melanoma. It concerned a type 1 metastasis in 11 patients. Symptomatology consisted mainly of gait problems (table 5.45). Gait ataxia may be correlated with a localization within the vermis, and a limb ataxia with a hemispheric lesion. Obstructive hydrocephalus was also noted on CT in all cases.

Table 5. 44 - Metastases to the Cerebellum
Presenting Symptoms in literature series

	Fadul All N=59	Solitary N=26	Ampil N=45
Symptoms			
Headache	59.3%	77.0%	44.4%
Gait disturbance	59.3	84.6	42.2
Dizziness	38.9	53.8	28.8
Nausea /Vomit.	40.6	53.8	13.3
Clumpsy limbs	13.5	18.3	--
Diplopia	10.0	19.2	4.4
Dysarthria	6.7	11.5	13.3
Deafness	1.7	3.8	--
Supratent.sympt.	15.2	--	--
Spinal cord sympt	1.7	--	--
NO SYMPTOMS	1.7	3.8	13.3

Imaging is certainly important in this setting. At CT a particular enhancement is noted. A marginated hypodense region is seen within a peripheral rim. An irregular complex thick ring or a dense lobular enhancement with a central hypodense component may also be observed (Weisberg).

Table 5. 45 - Solitary Cerebellar Metastases
Neurologic findings at presentation and diagnosis
(N=17) data of Weisberg

Symptoms		Signs	
Gait instability	11cases	Gait ataxia	17cases
Headache	6	Limb ataxia	12
Vomiting	6	Horiz.Nystagmus	6
Diplopia	3	Abducens paralysis	6
Dizziness	3	Papilledema	6
		Babinski sign	5
		Facial paralysis	2

Differential diagnosis with meningioma, ependymoma and medulloblastoma must be considered.

METASTASES to the BRAIN STEM

The brain stem is an important strategic neurological zone for motoric and sensitive neurologic functions. Any disturbance will result in a distinct deviation of the function of several of the cranial nerves and more distal activities.

Reports on metastases within the brain stem are very rare. Since the landmark report by Hunter et al. in 1968, based on a large autopsy series, only a few case reports and small reviews have appeared.

In the already mentioned autopsy data of Pickren et al., the incidence of brain stem metastases is very low and accords in fact with its very small volume. They found an overall incidence of 2.5% in the autopsied patients. It should be remembered that in that period, imaging methods were not available to visualize brain stem pathology as in present times.

In a series of 393 autopsy patients with brain metastases, Hunter et al. found 45 cases in which the brain stem was involved either as a tumor deposit or had been invaded by contiguous spread, or 11.7%, a relatively high figure.

Male patients were in the majority, nearly 2 to 1. The ages ranged from 30 to 85 years. The primaries involved are shown in table 5.46. Almost half of them were bronchogenic carcinomas, and represent the majority in both genders, while breast cancer scored high for women.

These selected data more or less confirms the major involvement of bronchial and breast cancer.

Table 5. 46 - Metastases to the Brain Stem
Primary involved (N=26)
Autopsy data from Hunter et al. 1968

	Male	Female	Percent
Bronchus	16	5	46.7%
Breast	--	6	13.8
Melanoma	2	2	8.9
Thyroid	2	--	4.5
Kidney	2	--	4.5

Also 1 case from colon, stomach, adrenal, prostate, cervix uteri and 5 undetermined cases.

A recent series was reported by Huang et al. It concerned 26 patients with brain stem metastases of a series of 421 patients with brain metastases or 6.1%. Midbrain was involved in 6 cases, while the other 19 cases had metastases in the pons. The reported patients were subjected to radiosurgery and are hence a selected group. The primaries involved are on table 5.47.

Table 5.47 - Metastases to the Brain Stem
Patients treated with radiosurgery
Primaries involved (N=25)
Data of Huang et al., 1999

	Male	Female	Percent
Bronchus	6	4	40.0
Kidney	4	1	20.0
Melanoma	3	1	16.0
Breast	0	3	12.0
Skin (squamous)	2	0	8.0
Larynx	1	0	4.0

Symptomatology of Brain Stem Metastases

The symptomatology of brain stem metastases can be somewhat misleading, as they can result in various neurological syndromes due to their strategic location. A number of symptoms can be due to other concomitant hemispheric metastases. The best data are from Hunter et al. and Huang et al. (table 5.48).

The most common signs are disturbances of consciousness, cranial nerve paralysis, pyramidal tract signs and cerebellar dysfunction. Headache is remarkably absent.

Another good analysis of the brain stem symptoms was presented by Ongerboer et al.

1. Mental symptoms are probably due to the interruption of midbrain connections with the limbic sys-

tem or to increased intracranial pressure due to internal hydrocephalus by compression of the aqueductus.

Table 5. 48 - Metastases to the Brain Stem
Symptomatology in two' large' series

	Hunter 1968 N=25	Huang 1999 N=25
Asymptomatic	7	--
Hemiparesis	11	11
Cranial nerve paralysis(')	14	8
nerve III	3 cases	1
nerve IV	2 cases	2
nerve V	3 cases	2
nerve VI	4 cases	4
nerve VII	4 cases	4
disturbance of conjugate gaze	3 cases	5
Ataxia	5 cases	8
Hemisensory loss	2 cases	2
Obstructive hydrocephalus	4 cases	1
Horner syndrome	--	1(")

(') more than one nerve can be implicated in any patient
(")both authors reported their results in the same format, a rare occurrence in the oncology literature

2. Conjugate upward gaze paralysis, loss of convergence and impaired reaction to light are supranuclear symptoms due to invasion of the different cranial nerve nuclei.
3. Specific nuclear symptoms are bilateral ptosis, dilated pupil and nystagmus.
4. Damage to the cerebellar connections causes disturbances of the coordination and hemihypalgeia contralateral to the oculomotor lesion.
5. When the tumor is located in the basal part of the brain stem-pyramidal tract symptoms can be observed.

Weiss et al. reported on three cases from melanoma, ovary and urinary bladder, while Ongerboer et al. reported one from a kidney and one from a breast cancer. Two other reports from the literature concern a bronchus and a breast cancer. Solitary brainstem metastases have been reported but are rare (table 5.49).

Table 5.49 - Solitary Brain Stem Metastases
Reported cases (Literature survey)

Netzky 1952	1 case bronchus cancer (autopsy)
Earle 1954	2cases(12 brain stem in 1498 autops.)
Earle 1954	3 cases (19 brain stem in 595 autops.)
Stevenson 1963	1 case breast cancer
Hunter 1968	1 case (45 brain stem / 393 CNS meta) kidney cancer
Weiss 1978	3 cases : melanoma, ovary and urinary bladder.
Ongerboer 1981	3 cases: kidney, breast and bronchus.

Derby et al. reported two type 1 metastases where brain stem symptomatology preceded the diagnosis of a bronchial and a renal carcinoma.
While brain stem metastases can be diagnosed on clinical grounds, CT and MRI are the mainstay for localization and confirmation of the diagnosis. When imaging features are atypical or not adequate, stereotactic biopsy can be indicated.

A prostate cancer patient presenting with Benedikt's syndrome has been reported by Loseke et al. Extrapyramidal hypertonia, and in particular abnormal choreo-athetoid movements as tremor are the main signs of this type of inferior red nucleus syndrome. At CT and autopsy, the single metastasis was confirmed as involving the mesencephalic tectum with destruction of both red nuclei.

A rare occurrence is the Wallenberg syndrome caused by metastatic involvement of the brain stem, particularly in the medulla oblongata. The syndrome consists of an ipsilateral altered sensation over the face, paresis of the palate and vocal cord with dysphagia and dysphonia, ataxia of the limbs, nystagmus and Horner's syndrome with contralateral loss of pain and temperature sensation in the trunk and limbs. Such metastases have been reported only rarely. A review by Ho et al. could retrieve 5 cases from the literature, of which 4 from a bronchial cancer and one of a melanoma. Kleinschmidt et al. added one from a malignant meningioma, primarily located in the left ventricle.

Strangely enough, the strategic importance of the brain stem for the respiratory control is peculiarly almost not implicated in metastatic symptoms. Most probably it is not noted in the terminal phase. Two cases have been reported where either hypercapnia or sudden drowsiness with other nerologic symptoms resulted in the dia-gnosis of an important solitary metastasis in the upper medulla (Corne et al., Rhodes et al.), both from an adenocarcinoma of the bronchus.

INTRARACHIDIAL METASTASES

Metastases within the vertebral (spinal) canal are not uncommon in oncology patients (fig.5.8). For clarity, a subdivision can be set up according to Barolat-Romana et al. (table 5.50). In several reports, distinction is not always made between the different metastatic locations.

Table 5. 50 - Metastases to the Vertebral Canal
Classification Modified from Barolat-Romana et al.

Intradural
1. intradural intramedullary
2. intradural extramedullary
   a. subarachnoidal
   b. intradural extraarachnoidal
   c. epidural with secondary invasion of meninges
3. leptomeningeal carcinomatosis

Epidural
1. only within epidural space
2. vertebral metastases with extension in epidural space
3. with extension along spinal nerve

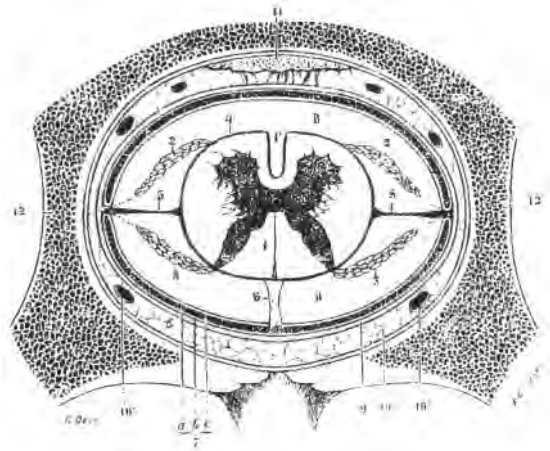

Fig.5.8 - Horizontal section of the spine and the intrachidial contents: 7: arachnoidea; 8: subarachnoidal space; 9: dura mater; 10: epidural space.

Although the clinical problems are somewhat similar, the diagnostic and therapeutic approaches and the prognosis is very different. In the last decades a relative increase of this entity has been noted. Several reasons have been put forward to explain this (modified from Barolat-Romana et al.):

1. a better awareness of the signs and symptoms;
2. increased performance of lumbar punctures;
3. improved techniques for CSF fluid analysis;
4. possible influence of better treatment of the primaries with longer survival, allowing presentation of metastases;
5. improved imaging capabilities.

Pathways

Although the dura mater is a strong membrane resisting to the spread of metastatic cells, invasion of it and the different compartments will occur in a number of patients.

Various pathways can be incriminated:

1. direct extension as from a vertebral metastases;
2. hematogenous either arterial or venous;
3. through the cerebrospinal fluid as for primary intracerebral tumors: ependyma, neuroblastoma, etc.;
4. perineural invasion from tumors towards the intrarachidial or intracranial content.

We will now discuss the following in turn:

Intramedullary metastases
Intradural extramedullary metastases
Epidural metastases
Leptomeningeal metastases

Symptoms relating to the three metastatic sites do not differ very much, but they can be distinguished (see further).

Intramedullary metastases have a relatively rapid progressive symptomatology. The onset may be acute, with paraplegia in a few days. Some think that hemorrhage and infarction play an important role.

INTRAMEDULLARY METASTASES

Hematogenous intramedullary metastases are rare. Based on the weight of the brain and spinal cord, one would expect an incidence of 2.5% for all cases of CNS dissemination, but it would appear much lower. When intramedullary metastases occur they are frequently accom-panied by other CNS metastases.

Drop metastases from primary brain tumors are more frequent on the surface of the medulla than intramedullary. Seeding down within the central canal with subsequent arachnoidal and subarachnoidal invasion and implantation in the medulla is common in ependymomas, medulloblastomas, malignant gliomas and pineal tumors.

There would appear to be two forms of intramedullary cord metastasis (Findlay et al.). The most common is discrete, well-defined intramedullary metastasis, almost certainly hematogenous in origin. The other one consists of a tumor involving the cord parenchyma through leptomeningeal invasion, arising either from embolic seeding through the CSF or direct extension from nerve roots or dura mater.

The data dispersed within the literature on the incidence of intramedullary metastases were reviewed by Costigan et al. There are serious discrepancies probably due to the registration method, diligence at autopsy and selection bias towards treated patients (table 5.51).

Table 5.51 - Intramedullary Metastases
Incidence data (review by Costigan et al.)

	Chason	Hashizume	Costigan
Autopsies N	---	11,362	7,330
N cancer eval.	1,096	433	627
N with CNS meta	18.3%	22%	24.4%
N with I.M.	10	5	13
as % of N w.canc	0.9%	1.2%	2.1%
as % of CNS meta	5.0%	4.2%	8.5%

As for most CNS metastases, the primary tumor involved is bronchial carcinoma followed by breast cancer. Most series are small. Many authors review the literature. The latest review is from Sander-Connolly et al. in 1996 (table 5.52).

From 180 autopsied cases, Hirano et al. mention 6 cases originating from bronchial cancers, two from breast and one malignant melanoma. The most frequent site or level of the intramedullary metastases is the thoracic level (table 5.53). More recent data, however, reveal that about half are at the cervical region (review by Findlay et al.). We are not aware of any study correlating the site of the primary concerned and the level of the metastases.

In a few patient,s the intramedullary metastases were associated with syrinx formation. Foster et al. reported on a M66 with a colon cancer and a F55 with a breast cancer, while recently Ateaque et al. reported a M63 with a renal carcinoma.

A type 1 metastasis at T-4 level, presenting with different peripheral motor weakness segments, was reported by Hirose et al. The evolution was dramatic leading to death within a few days. At autopsy, a squamous cell bronchial cancer was confirmed, as had already been suggested by radiology and the presence of malignant epidermoid cells within the CSF.

Table 5. 52 - Intramedullary Metastases
Primary Tumors Involved (N=174)
Literature Review by SanderConnolly 1996

Bronchus	54%	Colon	3%
Breast	13%	Thyroid	2%
Melanoma	9%	Various	8%
Lymphoma	5%	Unknown	3%
Kidney	4%		

Table 5.53 - Intramedullary Metastases
Site or level Involved

	Edelson N=70	Findlay N=148(')
Cervical	20%	45%
Thoracic	29%	35%
Thoraco-Lumb.	7.5%	
Lumbar	12.6	
Unknown(')	29%	

(') not stated in the reports used for review
(°) literature review1987

In a few patients, the intramedullary metastases were associated with syrinx formation. Foster et al. reported on a M66 with a colon cancer and a F55 with a breast cancer, while recently Ateaque et al. reported a M63 with a renal cell carcinoma.

Symptomatology

A careful neurologic examination is mandatory, as in all situations.
Pain is an important symptom and the first sign. It is initially in midback but soon evolves towards radicular pain. Although pain elicited by straight leg raising is more indicative of an extramedullary disease, it occurs in intramedullary tumors and metastases, probably because of some traction. Sensations of weakness in the legs and spasticity is present in more than half of the patients.

In more than half of the patients, a sensory level will occur, as well as paresthesia, sometimes with dissociated sensory loss, typical for intramedullary lesions. Bowel and bladder dysfunction is common but rarely as the first symptom (Edelson et al.) (table 5.54). A similar variation in symptomatology is reported by Grem et al. in a review of 5 cases and the literature up to 1985 (table 5.55). They make a distinction between the initial sign (first symptom) and the later status at diagnosis.
The metastasis has a low mass effect. The change in size can be very subtle and possibly only visualized by a faint size modification or by hypodensity evolving to a hyperdensity.
CT can observe the pathology, but MRI is much better suited for diagnosis as it visualizes the whole cord and may also detect variation in signal intensity (Zimmerman et al.).

Table 5.54 - Intramedullary Metastases
Symptomatology (N=38) Edelson et al. 1972

Pain local	42%	(All pain 65%)
radicular	34%	
Paresthesias	52	
Bladder or bowel	63	
Sensory level	71	
Dissociat.sensory loss	15	
Spasticity	60	

Table 5. 55 - Intramedullary Metastases
Neurologic symptomatology (N=55)
Literature review by Grem et al. 1985

Initial		At diagnosis	
Pain nonradicular	62%	Motor deficit (any)	100%
radicular	29	Sensory level (pain)	49
Motor deficit	64	Dermatomal sens.def	13
Paresthesia	27	Muscle atrophy	5
Bowel-Bladder	9	Bladder / bowel dysf.	71
		Upgoing toes(')	31
		Spine tenderness	8
		Leg raising pain	11
		Flaccid paralysis	45
		Spastic paralysis	9
		Brown Sequard	11

(') Babinski reflex

INTRADURAL Extramedullary METASTASES

These metastases lie in the subdural space, indeed a potential space, without any communication to the subarachnoidal space. It communicates, however, with the lymph spaces within the dura mater, the so-called 'dural lake', providing a free communication between both and the perineural lymphatic network. These perineural lymphatics are probably the principal avenues for spread.
Primary intracranial tumors are the most frequent source of extramedullary intradural metastases. The tumors of childhood such as ependymomas, medulloblastomas and other neuroectodermal tumors have a high frequency. Seeding is often present at diagnosis.
This situation is rare in adults. They are hardly mentioned in textbooks and only a few reports have been published.

The non-neuraxial intrathoracal or retroperitoneal tumor-cells probably enter the lymphatics, while seeding through the venous channels is much less frequent than for vertebral and epidural metastases (Borovich et al.).

They appear as spherical nodules adherent to nerve roots or the cord with filling of the pouch of subarachnoidal space along the outgoing nerve root. Sub-

arachnoidal metastatic deposits from tumors outside the neuraxis are rare. They can be single or multiple, discrete or presenting as a diffuse infiltration only demonstrated on microscopic slides.

Myelography is indicated as it will indicate filling defects. Asymmetric and irregular encircling of the cord with widening of the cord shadow has been described, as well as complete obstruction. Invasion of the extra-arachnoidal space was clearly a direct spread of the tumor along the roots of the lumbar nerve in the case of Barolat-Romana et al. The same authors stress the difference between centripetal tumor spread through the neural foramina by way of the perineurium (perineural spread) leading to an intradural extra-arachnoidal metastasis, and centripetal spread through the lymphatics leading to leptomeningeal and subarachnoidal space involvement or leptomeningeal carcinomatosis. Most of these patients have also cerebral or cerebellar metastases, so that these metastases can be considered as tertiary, following the cerebrospinal fluid circulation. The low level with entangling of the cauda equina in several cases supports this mechanism.
The few case reports are grouped within table 5.56.

Table 5.56 -Intradural-Extramedullary Metastases Literature Review

Author	Inc(*)	Patient	Primary	Level
Wilson 1947	2/53(**)			
Chandler 1954	2/49			
Rogers 1957	1/17	M54	Adrena	D4
Wright 1963	1/81			
Beehler 1965	1/25	F55	Breast	D6-D7
Feiring 1965		F56	Breast	C7-D4
Feiring 1965		F52	Breast	C6-D2
Edelson 1972		M50	Bronchus	Thor.
Constans 1973		F61	Melanoma	C5-C6
Mohlen 1978		F57	Breast	C7-D1
West 1979		F74	Breast	D11
Kim 1980		M66	Colon	C3-C6
Borovich 1981	3/130	F63	Breast	D2-D3
		M38	Apudoma	D9-10
		M29	Neuroblas	C4-C6
Mondal 1981		M68	Esophagus	L1
		F73	Breast	L2-L4
Hirsh 1982		F32	Breast	C6-C7-T1
Perrin 1982	10/200	10 cases		all below Th10
	(breast 4, bronchus 3, melanoma 2, uterus 1)			
Barolat 1983		M62	Unknown	L2-L5
Auque 1985		F50	Breast	L2-L4
		M52	Bronchus	L2-L3
		M45	Melanoma	C3-C6
Barloon 1987		M55	Un.Adenoc.	L2-L3
		M60	Kidney	diffuse
Pelissou 1989		M71	Prostate	cauda
		M56	Unknown	C6-C7
		M49	Unknown	L3
Stambough 1991		M73	BronchusSC	L4-L5
		M54	Prostate	L2
All	(20/555)			

(*) of spinal intradural metastases
(**) this and the next 6 reports were not available to us

On this table are noteworthy the high number of breast cancers (13), bronchial carcinoma (6) and melanomas (4). Three were from an unknown primary, even after autopsy, type 1 metastases. Borovich et al. mention kidney, ovaries and adrenal tumors as primaries.

Symptomatology

These metastases manifest themselves in very similarways to epidural metastases.
Pain, local or radicular, is present in almost all patients. Motor function is impaired in all patients as a clear sensory level. Dysfunction of the bladder or bowel is also present in almost all cases. Local tenderness over the involved spinal segment was reported in 8/10 cases mentioned by Perrin et al.
The same authors list a number of differences compared to the symptoms of extradural (epidural) metastases: They give rise to prominent pain which is experienced at an earlier stage and is characteristically more severe and crampy in nature. Radicular distribution is prominent. Remarkable is that bladder and bowel dysfunction is also much more - twice- present than with epidural metastases. Imaging of the bony vertebral column is usually completely normal.
CT enables a detailed in vivo detection and can show silent spinal subarachnoidal metastatic deposits.

Metastases to the Cauda Equina

A particular group of patients have metastases within the cauda equina. Pellisou reported one case, but Fearnside et al. reported 8 cases in 1978 of 70 consecutive patients with a tumor in the cauda, or 11.5%. Four of them were drop metastases from two medulloblas-tomas and two oligodendrogliomas. Four other were extracranial tumors: two from the breast, one bronchial and one reticulosarcoma.
An important number of the reported cases concern indeed several intracranial and hypophyseal malignancies.
Intradural sacral nerve root metastasis can mimic the symptomatology of a hernial disc.

A few cases have been published. An unusual case was reported by Newton et al., in a man of 48, where two years after the diagnosis of an extensive ethmoid carcinoma, an extradural tumor from L5 to S2 was diagnosed at surgery.
A women of 51 was reported presenting with low back pain and intense pain in the thigh to the lateral calf with numbness. At surgery, metastatic adenocarcinoma was found in the cauda equina. Subsequently an endometrial adenocarcinoma was found (Hargraves et al.).

Epidural Metastases

Extra or epidural metastases are relatively frequent and have different origins (table 5.57). A distinction be-

tween the modes is rarely made in the reports. They are usually considered vertebral (spinal) bone metastases. The main problem is spinal cord compression (fig.5.9).

The presenting symptoms are very similar tor vertebral problems, and in some aspects different from other problems. Caraceni et al. outlined the subtle differences which, unlike the others, are more indicative of an epidural pathology (table 5.58).

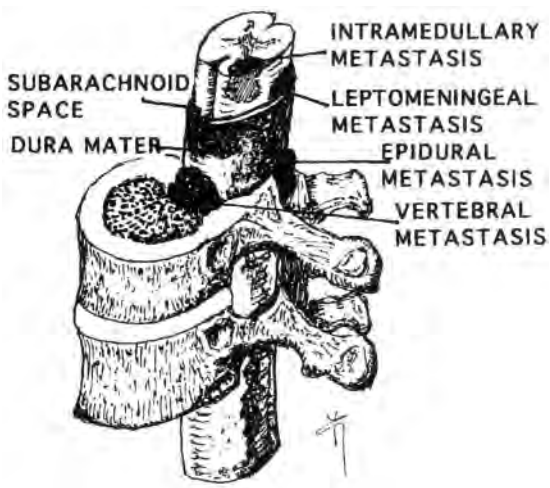

Fig.5.9 - The different locations of metastases 'around' the spinal cord

Table 5. 57 - Epidural (Extradural) Metastases Pathways

1. Hematogenous, paravertebral and epidural plexus venosus
2. Direct extension of mediastinal or retroperitoneal masses or nodes through the intervertebral foramina
3. Transcortical extension from metastatic disease in the vertebral corpus (bone metastases).

Table 5. 58 - Epidural Metastases Presenting symptomatology (Caraceni et al.)

1. Sudden pain exacerbation, difficult to control with increasing doses of analgesics (crescendo).
2. Pain worsens with recumbency.
3. Pain worsens with cough and Valsalva maneuver.
4. Pain with radiculopathy.
5. Lhermitte sign positive.
6. Pain of funicular type.

We will discuss them later in relation to the vertebral metastases, as almost all have some connection with them.

LEPTOMENINGEAL CARCINOMATOSIS

Various other names have been given to this situation, including meningeal metastases, carcinomatosis or carcinomatous meningitis. More frequent than intramedullary or intradural metastases, leptomeningeal carcinomatosis is not an uncommon clinical problem. Some authors have stressed that it is more frequently diagnosed in the most recent decades, maybe due to the longer survival of most treated primaries, but certainly also due to earlier and prompt diagnosis and to the availability of adequate imaging facilities. Several type 1 metastases have been reported.
Leptomeningeal carcinomatosis is usually a late complication of any cancer, but one should keep in mind that it is in 10 to 15% of the cases - the presenting manifestation of an unknown tumor, of which many will not be detected even at autopsy. This pathology must be taken into consideration at any stage of an oncology patient, even in patients who had never previously been treated for a malignancy.

Leptomeningeal carcinomatosis has become more frequent in several cancers for which chemotherapy has resulted in a long remission or/and in a delay of metastatic spread and/or growth. The penetration of cytostatic drugs in the CNS is low, resulting in a 'sanctuary' situation allowing further proliferation of tumor cells within this compartment.
The infiltration of the leptomeninges by cancer cells can be focal, multifocal or diffuse. Several clinical forms have been distinguished and described.

Pathways

The possible pathways the cancer cells can follow to give rise to this type of metastases, which is commonly invisible to the naked eye and imaging methods, has been extensively discussed in the literature. However more hypotheses have been put forward than adequate pathology studies performed.
The landmark study of Kokkoris has determined that several routes are followed, more or less depending on the type rather the site of the primary tumor (fig.5.10).

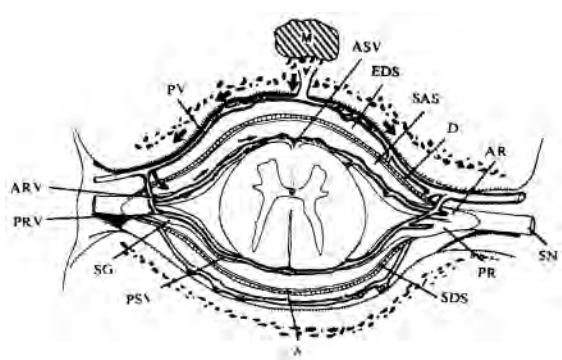

Fig.5.10 - Probable routes towards leptomeningeal metastasis in breast or bronchial cancer. The route is indicated by arrows. M: metastasis; PV: paravertebral veins,; ARV: anterior radicular vein; PRV: posterior radicular vein; SG: spinal ganglia; PSV: posterior spinal vein; A: arachnoid; SDS: subdural space; PR: posterior route; SN: spinal nerve; AR: anterior route; D: dura mater; SAS: subarachnoid space; EDS: extradural space; ASV: anterior spinal vein. (From Kokkoris, with permission)

For breast and bronchial carcinoma, leptomeningeal spread is the result of propagation of cancer cells from vertebral or paravertebral metastases. After having reached the bone marrow, cells will spread along intravertebral veins, extending via the (epidural) paravertebral veins to reach the dura and arachnoidal sleeves of nerve roots before reaching the subarachnoid space. From there, it is presumed that they will enter the leptomeninges, especially the subdural surface. A further dissemination along the fluid is then likely. Malignant nodules along the nerve roots or proximal parts of the spinal nerves is the rule, due to centrifugal migration of cancer cells. Gastrointestinal cancer presumably metastasizes via the perineural routes.

Table 5.59 - Leptomeningeal Carcinomatosis
Pathways of tumors to leptomeninges
Modified from Grossman et al.

1. Infiltration of leptomeninges through arachnoid vessels or choroid plexus after hematogenous dissemination
2. Direct extension from pre-existing CNS tumors (epidural, subdural or intraparenchymal)
3. Direct extension from pre-existing systemic tumors following peripheral nerves to subarachnoidal space (perineural spread)
4. Seeding of subarachnoid space during surgical extirpation of intraparenchymal tumors.

The perineural route is the usual pathway for head and neck tumors, although this is not frequently observed (Rotman et al.; Debois).
Other cases result from spreading along the arterial route taken by cells from deep brain or medullary metastases as initial stage. Leptomeningeal cancer could however result from communication of concomitant cortical or subependymal metastases with the subarachnoid space or the ventricles. Only a small proportion of cases are due to cancerous invasion of the pia-arachnoid.
Summarizing, one can state that most cases result from spread from axial, mediastinal or retroperitoneal, nodes and blood vessels through intervertebral and possibly cranial foramina via perineural and perivascular pathways to the leptomeninges (table 5.59).

Incidence

Cancers of the adenocarcinoma type are the most frequently involved. Some authors have remarked that the involved primaries have also changed. Breast, bronchial of all histologies and stomachal are the most frequent, although it seems that the latter is now less frequent. Its incidence is indeed also decreasing.

The exact incidence is unknown but figures of 3 to 5% of patients with solid tumors are usually mentioned. For small cell carcinoma of the bronchi it probably amounts to between 11 and 18%. Quite a number present as first symptom (type 1) of whom a lot have an undetermined primary, even after autopsy (see further).

Primaries Involved

Several quite large series have been reported which mention the type of primary involved.
When 6 large series are considered and summed up, totalling 234 cases of solid tumors, breast cancer is the most prominent primary with almost half of the patients, followed by bronchial cancer and to a lesser degree by malignant melanoma (table 5.60).

Table 5. 60 - Leptomeningeal Carcinomatosis
Limited Literature Survey of large series
Summing-up of data collected by Formaglio et al. 1998

Breast cancer	104 (44.4%)	Head-Neck	13
Bronchial cancer	61 (26.1%)	GenitoUrinary	12
Melanoma	24 (10.2%)	GastroIntest	10

(Grouping the series by Gonzalez, Posner, Wasserstrom, Sause, Kaplan and Chamberlain.

It will be noticed that genital and urinary cancers are very rare as primaries of leptomeningeal carcinomatosis. A few ovarian cancers have been reported (Bakri et al.). There have also been a number of case reports or small series, including several type 1 cases. We have grouped them on table 5.61. Several other primaries are mentioned, probably reported due to their 'uniqueness'.

Gender distribution is almost never given. On reporting 41 LM-patients from solid tumors, Stardy et al. remarked that breast cancer was the leading cause in women (18/20) and bronchial cancer in men (11/21).

Pathology

In some cases, the brain, spinal cord or nerve roots appears will be coated by a thick layer of tumor tissue. In other cases only a slight meningeal opacity might be perceptible. This is most visible over the sulci, where it may make the blood vessels less distinct in appearance. The basal surface, the anterior portion of the sylvian fissure, the chiasmatic cistern, the interpeduncular fossa and the cerebellopontine angles are usually the most prominently marked. Around the spinal cord, this is more appreciable on the dorsal surface.

Table 5.61 - Leptomeningeal Carcinomatosis
Limited Literature Survey of small series (*)

Stomach	14 (4)(**)	Thymoma	1 (-)
Bronchial cancer	6 (1)	Bile duct	1 (-)
Breast cancer	4 (0)	Ewing sarcoma	1 (-)
Gallbladder	4 (2)	Melanoma	2 (-)
Rectum	3 (1)	Tonsil	1 (-)
Prostate	2 (1)	Tongue	1 (-)
Unknown	2 (1)		

(**) between parenthesis the number of type 1 metastases)
(*) reports by Moberg (1960); Havkins (1963); Dinsdale (1964); Kupffer (1965); Fisher (1979); Stark (1986); Debois (1987); Leonardi (1992); Gasechi (1992); Bitouk (1993).

Infiltration around the brain stem will involve the

cranial nerves, often a prominant symptomatology.
The characteristic finding will be a diffuse or multifocal infiltration of pia mater and arachnoid membranes, with cells filling the subarachnoid space. The cells are either as in a single layer or thicker aggregates. The growth pattern will reflect the histology type of the primary. Zones of demyelination are common in the zones of fibrosis. Invasion of the parenchyma is present in about half the patients. Dinsdale et al. have made some excellent diagrams of this (fig.5.11 & 5.12).

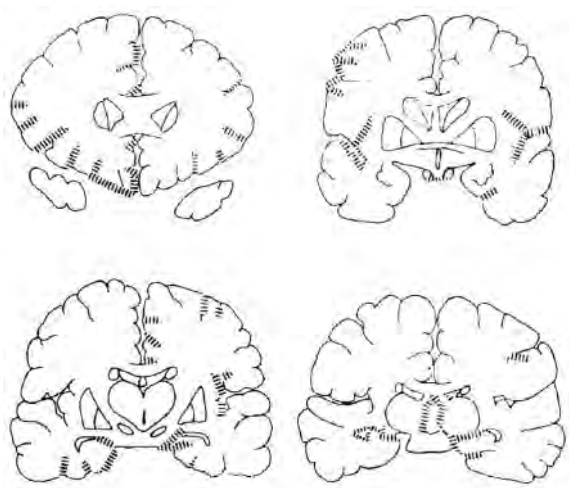

Fig. 5.11 - Schematic drawing of surface coating by leptomeningeal metastases over the brain as seen from transverse sections (with permission from Dinsdale et al.)

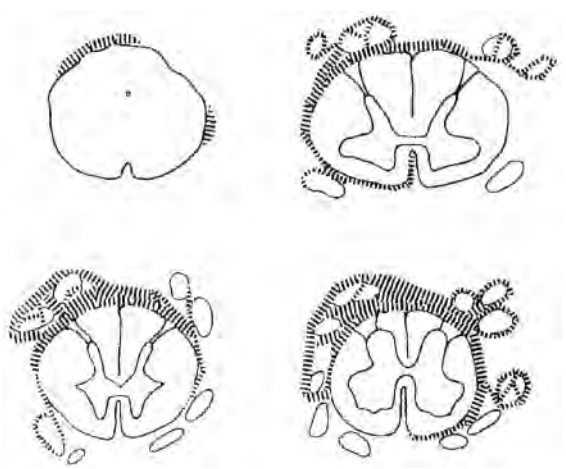

Fig.5.12 - Schematic drawing of the surface coating by leptomeningeal metastases over the spinal cord as seen from transverse sections (with permission from Dinsdale et al.)

Symptoms

As the entire neuraxis may be seeded by the metastases, symptoms can be very variable. They are usually multifocal and diffuse over the whole surface of the brain an the length of the spinal cord.

The simultaneous occurrence of symptoms and signs at more than one level of the cerebrospinal system is the hallmark of the clinical presentation. The symptoms can be separated into cerebral, cranial nerves and spinal.
The point must be made that in several patients, other systemic metastases can be present, complicating or obscuring the symptomatology.The symptomatology can be di-vided into three groups, and four evolutive groups can be distinguished (Stammler et al.) (table 5.62).
The onset of symptoms and signs is usually gradual and insidious. Several authors have reported signs and symptoms for their respective patient series. There is almost no difference between them. The best documented and often referred to and cited data are from Wasserstrom et al. (table 5.63). Certain progressive stages can be discerned:

1. headache and occasional nausea and vomiting;
2. increase in headache associated with mental disturbances, beginning ocular palsies and finally meningeal irritation;
3. increase of all preceding symptoms, rapid deterioration of mental status, meningeal involvement, leading to death.

Table 5.62 - Leptomeningeal Carcinomatosis

Symptomatology Groups
1. Symptoms from cerebral hemisphere involvement
2. Symptoms from spinal cord involvement
3. Symptoms from cranial nerve involvement
4. Multilevel dysfunction

Evolution Patterns
1. Polyneuritic - polyradicular syndromes, possibly combined with medullary symptoms.
2. Evolutive cranial nerve dysfunction.
3. Predominant meningitic evolution
4. Progressive brain and cognitive dysfunction.

One of the most common initial symptoms, occurring in more than half of the patients, is neck and/or back pain. The last is commonly overlooked and taken for a spinal problem. Headache is also very frequent but less than neck or back pain. The headache is variable in its appearance and can be focal, diffuse, in the occipital zone, and sometimes bifrontal. It may mimic migraine or cluster headache.
A wide spectrum of mental status modifications or disturbances has been reported. Loss of consciousness, seizures, even hallucinations and coma are rare but described as a first sign.
At neurological examination, the most frequent observation is cognitive impairment with reduction of vigilance. Wide-based ataxic gait is also frequently observed. A typical part of the syndrome, though only occurring in one third in the beginning, are cranial nerve symptoms. A further third will present during further evolution.
Ocular nerves (ophthalmo-paresis) and facialis are the most frequent. They can also appear as a first sign.

Table 5.63 - Leptomeningeal Carcinomatosis
Signs and Symptoms in 90 patients with solid tumors (Data of Wasserstrom et al.1982)

Cerebral (N=45)				Cranial Nerves (N=50)				Spinal (N=74)			
Symptoms		Signs		Symptoms		Signs		Symptoms		Signs	
Headache	30	Mental change	28	Diplopia	18	Paresis III,IV,VI	18	Motor Weakness	34	Reflex assym	64
Mental change	15	Seizures	5	Hearing loss	7	Facial weakness (VII)	15	Paresthesias	31	Weakness	54
Walking difficulty	12	generalized	3	Visual loss	5	Hearing dimin.	9	Radicular pain	19	Sensory loss	24
Nausea-Vomiting	10	focal	2	Facial numbness	5	Optic neuropathy (II)	5	Back-Neck pain	23	Staright-leg R	11
Unconsciousness	2	Papilledema	5	Decreased taste	3	Trigeminal neuropath	5	Bowel-Bladder	12	Reactal hypotonia	10
Dyspahsia	2	Diabetes Insip.	2	Tinnitus	2	Hypoglossus probl.	5			Nuchal rigidity	7
Dizziness	2	Hemiparesis	1	Hoarseness	2	Blindness	3				
				Dysphagia	1	Diminished gag(IX,X)	3				
				Vertigo	1						

Radicular deficits at one or more non-contiguous levels can dominate the clinical picture and are the hallmark of the syndrome Mental symptoms are described in all series in terms of apathy, weakness, somnolence, lethargy, disorientation, impaired consciousness, defective attention, memory defects, confusion, stupor, mutism, hallucination, delirium, agitation, excitement, mania and psychosis (Bakri et al.). These include motor and/or sensitive deficits such as weakness, paresthesia, instability of gait and sometimes bladder and bowel problems (Review by Formaglio et al.).The clinicopathologic mechanism of the symptoms in cases of leptomeningeal carcinomatosis are set out in table 5.64 (Grossman et al.).

Table 5. 64 - Leptomeningeal Carcinomatosis
Clinicopathology of Symptoms
Modified from Grossman et al.

Increased intracranial Pressure:	Obstruction of normal CSF flow pathway
Focal Neurologic deficits:	Infiltration of nerves at crossing of subarachnoid space
Stroke-like syndromes:	Occlusion of pial blood vessels traversing the subarachnoidal space
Seizures:	Irritation or invasion of underlying brain parenchyma
Encephalopathy:	Interference with normal CNS-metabolism

Cranial nerve palsy might an the initial sign of LM (Reviewed by Kahn et al.). While this is not frequent, it can encompass every cranial nerve, mostly VIII and VII. Chamberlain reviewed the symptomatology at different presentation in 6 reported series, according to the different domains of neurological disturbances. The various data are on fig.5.13.

Rare presentations are first sudden deafness or sudden blindness, one only as type 1 presentation. Up to 1992, VonCampen et al. were able to find 20 cases in the literature. Since then we found 7 more cases. The primaries involved are in table 5.65.

One remarkable aspect is the presence of 7 stomachal cancers, but also 8 with an unknown primary, in fact type 1 metastases. Two additional cases from a bronchial adenocarcinoma have been reported by Kahn et al.Two patients presenting with a facial palsy were diagnosed with a leptomeningeal carcinomatosis from an un-known bronchial and stomachal cancer (Schneider et al.).

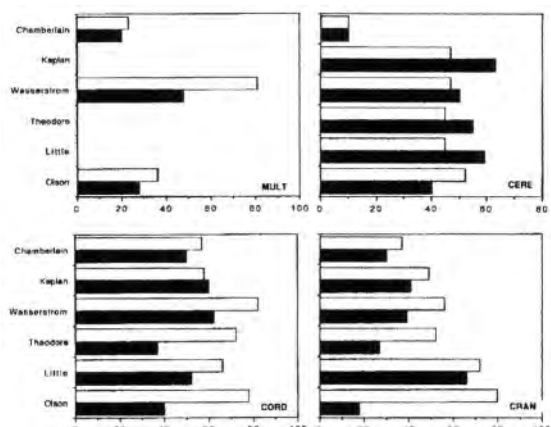

Fig.5.13 - Comparative incidence (%) of the involvement of the different domains in leptomeningeal carcinomatosis as reported in 6 literature series (black block at first diagnosis, white at evolution) Drawn from data by Chamberlain et al.

Table 5.65 - Leptomeningeal Carcinomatosis
Sudden Deafness presentation
Primaries Involved
Literature review (Van Campen and the author)

Stomach	9	Melanoma	1
Breast cancer	4	Unknown	8
Bronchus	4	Esophagus	1
Kidney	1		

Although gaze-evoked tinnitus is considered a symptom occurring after surgery on posterior fossa tumors, one patient has been reported in whom this was the first sign of an extensive cerebral and meningeal metastasis from a previously treated malignant melanoma. Unfortunately no autopsy confirmation was obtained (Caraceni et al.).

Patients with LM can develop cerebral ischemic complications. A partial obstruction of vessel by tumor cells has been invoked, as well as 'rarefaction' of the parenchyme surrounding the Virchow-Robin spaces infiltrated by the tumor. Multifocal arterial narrowing

to extensive perivascular tumor-associated vasculopathy may also play a role in the cerebral deficits encountered in these patients (Klein et al.).

Type 1 Leptomeningeal Carcinomatosis

The appearance of leptomeningeal carcinomatosis can be very insidious. The clinical pattern is not easy to describe and knowledge of a previous treament for a primary solid cancer can be very helpful to suspect the problem.
Diagnosis may be difficult and often delaying treatment. On the other hand, the availability of better diagnostic imaging methods probably now makes possible an earlier diagnosis.

There have been, however, several reports where the diagnosis of leptomeningeal metastasis preceded the diagnosis of an asymptomatic or undiagnosed malignancy, sometimes only uncovered at autopsy. A series specifically addressing the first presentation was reported by Bigner et al. in 1984, and was based on 220 patients, of whom 25 were considered to be first presentation (11.3%). In their series, the majority were bronchial cancers. (table 5.66).
The rate was different according to the type of tumor considered. It was very low in lymphoma, confirming that lymphomas almost never 'start' in the CSF. Primary neoplasms with leptomeningeal seeding present in half of the cases first with positive cytology. The main tumors presenting first with leptomeningeal carcinomatosis were small cell and adenocarcinoma of the bronchus (5), two stomachal, one melanoma and 8 indeterminate or unknown primaries.

Table 5. 66 - Leptomeningeal Carcinomatosis
Initial Presentation of the Malignancy
Series of Bigner et al. 1984

	N	% initial
Leukemia-Lymphoma	108	2
Extraneural Neoplasms	98	16
CNS Neoplasms	14	50

We found several reports in the literature (table 5.67) of type 1, some primaries only found at autopsy. There is a remarkable high number of gastric cancer (11), well known for its propensity to leptomeningeal carcinomatosis, but also of the less frequent gallbladder cancer. We do not claim completeness, but the data are indicative of its insidiousness. Bigner et al. have reported on a series of 25 extraneural cancers, first diagnosed by CSF-cytology because of their L.M. presentation.

The most helpful parameters for the diagnosis are age of the patient, the location of the lesions and the cytology reflecting the primary involved (Bigner et al.). They point out that an adenocarcinoma of unknown origin can be confused with a choroid plexus carcinoma.

Diagnosis

A definite diagnosis will result from the addition of
1. meningeal irritation symptoms;
2. dysfunction of cranial nerves concomitant with spinal (medullary) symptoms;
3. the presence of malignant cells in the cerebrospinal fluid;
4. knowledge of a previous treatment of a malignancy.

Tabe 5.67 - Leptomeningeal Carcinomatosis
Type 1 presentations
Literature Review by the Author

Primary unknown before diagnosis of LM		
Olsen 1974		bronchus(2), kidney, unknown
Appen 1978	M53	bronchus adenocarcinoma
Pissas 1981	F47	stomach cancer
MacCrary 1986	F60	stomach cancer
VonCampen 1992	M64	bronchus epidermoid
Schneider 1992	M53	bronchial cancer
Birouk 1993	M53	stomach cancer
Birouk 1993	F56	gallbladder
Deeb 1997	M53	stomach cancer
Diagnosis of the primary at autopsy		
Brucher 1960	M46	stomach cancer
	M52	bronchus cancer
	M42	stomach cancer
	M64	gallbladder
	M61	bronchus
	M66	stomach cancer
	F62	bronchus cancer
	M57	primary not found
	M52	stomach
Hawkins 1963	M67	gallbladder carcinoma
	F40	rectal adenocarcinoma
Groves 1991	M52	stomach cancer
Civantos 1992	M68	esophagus carcinoma
Schneider 1992	M51	stomach cancer
Patri 1997	M64	stomach cancer

The most important and first step in the diagnosis is the finding of malignant cells in the cerebrospinal fluid. Fluid cytology must be examined and eventually repeated whenever the leptomeningeal spread or pathology is suspected. This is positive in about 75% at the first punction, but must be repeated in cases of strong clinical suspicion. This will yield another 15%, but about 10% or less will still have repeated negative cytology.
The presence of cells foreign to this environment and either of a specific type (myeloma) or with 'malignant characteristics' will be highly indicative and ultimately diagnostic.

The finding of malignant cells in CSF, proves that tumor cells have reached the subarachnoid space or ventricular cavity followed by leptomeningeal seeding. Cases have been described where only microscopic metastases were found at autopsy, without positive CSF fluid cytology (fig.5.14).

Three general criteria for detection of neoplastic cells

in CSF can be posited (Bigner et al.).

1. The cells are foreign to their environment;
2. The cells are of a specific cell type;
3. The cells can possess 'malignant criteria', such as large size, large nuclei, a high nuclear-cytoplasmic ratio, multiple nucleoli, pleomorphism.

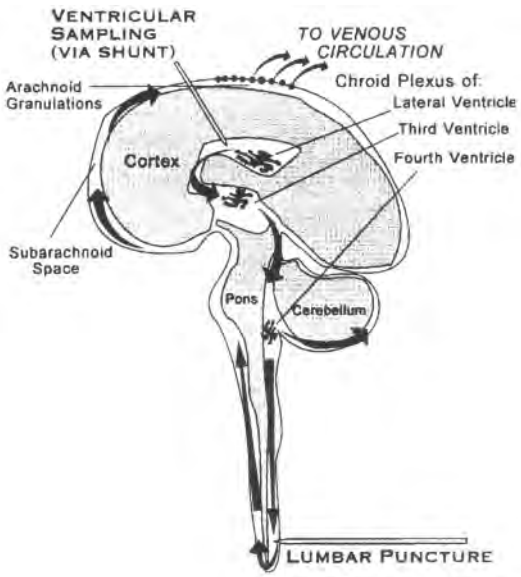

Fig.5.14 - Flow of cerebrospinal fluid, also called the third circulation, as indicated by the solid arrows. The sites for ventricular and lumbar puncture are indicated (from Watson et al., with permission)

The dosage of tumor markers has been extensively studied and discussed, but apparently not very sensitively or conclusively. CEA, PSA and AFP have all been dosed and are elevated in large parts of the concerned primaries. HCG and AFP are valuable in the diagnosis of disseminated gonadal tumors. Ca125 and Ca15.3 have been found in cases of respectively ovarian and mammary cancer and even serotonine in cases of carcinoid meningitis.

One study has examined the possibilities of β-Glucuronidase (βG) and Carcino-Embryonic Antigen (CEA). Both substances detect the presence of leptomeningeal infiltration, but not in case of lymphoma. βG is, however, also elevated in infectious meningitis (Schold et al.).

In some patients the placement of a ventricular shunt to relieve intracranial pressure is indicated. Where there is suspicion of LM, specimens of fluid taken at the shunt can be diagnostic, although examination of lumbar CSF is still clearly superior, at least in children. In a few patient, only shunt CSF was positive (Gajjar et al.).

The biochemistry of the fluid in leptomeningeal metastases can be indicative when cytology is neg-tive, as hypoglycorachia or elevated protein. Hypoglycorachia, defined as less than 60% of the serum level, is present in about half of the patients. This is correct only when serum levels are above 40 mg/dL. Protein levels are elevated due to blood brain barrier disturbances. The normal values for the commonly dosed substances in the CSF are given in table 5.68.

Table 5.68 - Cerebrospinal Fluid
Commonly dosed substances - normal values
Data of Watson et al.,1995

	CSF	Serum
Sodium, mmol/L	138	140
Potassium, mmol/L	2.8	4.0
Calcium, mmol/L	2.1	4.8
Chloride, mmol/L	119	103
Bicarbonate, mmol/L	22	26
Glucose, mg/L	600	900
Lactate, mmol/L	1.6	1.0
Total protein, mg/L	350	70
β_2-microglobulin, mg/L	1.1	1.9
Neuron Specific enolase, mg/L	6.5	
S-100 protein, pmol/L	406	
Myelin basic protein, mg/L	<4	
Lactate dehydrogenase, U/L	10.5	150

Several other substances have been studied but none has been revealed as specific or diagnostic. Beta-2-microglobulin has been found to be nonspecific and insensitive in the diagnosis of non-hematological LM. Lactate dehydrogenase (LDH) is also non-specific, but certainly enhanced when leptomeningeal involvement is present. The same is true for creatinine kinase, while elevation of neuron-specific enolase is aspecific (Watson et al.).

Imaging

Imaging plays a more definite role than a few decades ago, due to the development of CT and especially of MRI.

Diagnostic are a meningeal contrast enhancement and an enlargement of ventricle or sulci. It can be seen in cerebral and spinal regions, and is probably due to lesions of the BBB. False-negative images have been obtained, both with CT and MRI.

True meningeal thickening in the spinal cord, with the so-called sugar-coated appearance or with subarachnoid nodules is readily detected. This is frequent in the cauda equina

The progress of MRI technology and the gadolinium-enhanced contrast has made possible to reveal LM in a large number of the patients, even with negative cytology. This is especially the case when most of the enhancement lies against the skull vault (Watanabe et al). It can now replace myelography-CT as it is more sen-sitive and less invasive.

Cranial imaging can also show tumor infiltration of the cranial nerves as an enlargement of the nerves.

Gamma-imaging with the radionuclide ^{111}In-DTPA of the CSF-flow has received relatively less attention. It is very sensitive to detecting abnormalities in the flow. In Grossman's study, 70% of the patients with

LM had abnormalities in the flow study, of whom 30% over the cerebral convexities. The presence of tumor growth within the spinal canal will arrest flow and result in some compartimentalization earlier than MRI, when the tumors are still too small to become visible in the latter method.
Comparative data between CT and MR were studied by Krol et al. They observed that at least for LM, MR seems less sensitive (table 5.69).

Table 5.69 - Leptomeningeal Carcinomatosis
Imaging Features observed at CT-MRI in 39 patients
Data of Krol et al.

Pathology	CT	MRI
Abnormal contrast enhancement	9	3
Basal cisterns	6	1
Tentorium	8	2
Peripheral cisterns	6	1
Cortical sulci	5	0
Obliteration of sulci	9	2
Intraventricular masses	3	3
Subarachnoid space masses	2	2
Enlarged ventricles	13	13

Several pathology features are less well detected on MR. Consequently 44% of the CT and 65% of the MRI were interpreted as normal. They concluded, however, that T1W images are superior to T2W in depicting changes due to meningeal metastases. Intraventricular and subarachnoid tumor deposits, indicating advanced disease, were the only features with a positive MRI, evidence of meningeal seeding in the CSF-space.

The imaging features observed in 41 patients with LM (27 breast cancers) by Collie et al. are shown in table 5.70. It will be observed that no feature is dominant and that several signs must be looked for to make the diagnosis of LM.

Chamberlain et al. have evaluated the different imaging methods according to the presenting symptomatology syndrome (table 5.71).

Table 5.70 - Leptomeningeal Carcinomatosis
Imaging Features observed at CT-MRI (N=41)
Data of Collie et al.

Normal		6%
Hydrocephalus		13
Pial enhancement		35
Linear	32%	
Micronodular	54%	
Loculated enhancement		10
Subependymal deposits		7
Neural deposits		11
Cranial nerve	9%	
Cauda Equina	20%	
Dural enhancement		4
White matter high T2 signal		6
Parenchymal metastases		17
Bony metastases		5

Overall, radionuclide flow studies are most sensitive to detection of flow interruption due to tumor seedlings, while the other imaging methods are more sensitive to detection of nerve root thickening, cord enlargement, subarachnoidal nodules, intraparenchymal cord tumor and epidural spinal cord compression.

Table 5. 71 - Leptomeningeal Carcinomatosis
Abnormalities in Imaging depending on Clinics
Modified from Chamberlain et al. (N=61)

	N	%	Abnormal studies at CT-M	S-MR	FS
Asymptomatic	14	23	0	1	1
Cerebral	3	5	1	3	2
Cranial nerve	21	34	7	5	6
Spinal Cord	30	49	16	15	18
Multi-level	6	10	5	4	6

CT-M: CT-myelography, S.MR: spine MR with contrast; FS, radionuclide flow-study

Electromyography (EMS) has received rather limited attention in the diagnosis of LM, probably due to the dominance the fluid cytology. Radicular deficits in isolation are a difficult group, but the patients have abnormalities of motor nerve conduction with a reduced maximal conductive velocity (MCV) and abnormal prolonged F-wave latencies in the leg with normal peripheral nerve studies. As such, they are clearly distinguishable from other neurological disturbancies (Argov et al., Kaplan et al.).

Differential Diagnosis

Not every neurologic complaint in a cancer patient will be metastatic. It must, however, be suspected until proven otherwise.
Many neurologic diseases may be present and any thorough neurological examination with additional tests should disclose it. A number of benign situations are, however, close to central nervous system metastases. A differential diagnosis deserves some comment. Radiation myelitis (RM), necrotizing myelopathy (NM) and leptomeningeal carcinomatosis (LM) may be distinguished from intramedullary metastases (ISM) according to a number of signs, that nevertheless are not absolutely specific. This has been thoroughly discussed by Winkelman et al.

The presence of pain that is early in the onset - 'abrupt' and prominent in the clinical situation is more indicative of ISM, while it is more insidious, slowly progressive in radiation myelitis. Pain is almost not present in necrotizing myelopathy. In ISM the pain is localized at one level with a rather sharp level sign, while it is mostly diffuse and at several levels in LM.
Progression is slow in RM, relentless in ISM and LM and slow in NM. During progress new locations usually appear in LM, together with cranial nerves and hydrocephalus. There are no downward longtract symptoms.

In ISM, as already mentioned, there is a clear level line, and there are long tract signs below without any abnormality above, except in cauda equina syndrome or when root pain is present. New sites can appear or fast progression can occur. Necrotizing myelopathy can extend progressively either upwards or downwards and result in paraplegia.
Radiation myelopathy will correlate with the irradiated site and will depend on the dose-time factors, but any radiation in history does not exclude a metastatic problem (Margolis et al.).
The diagnosis of one metastatic site does not exclude the presence of any other, as leptomeningeal metastases can accompany intramedullary or cerebral metastases (Weissman et al.).

Leptomeningeal Metastasis in Children

Leptomeningeal metastases have been documented in children in a variety of tumors. It occurs more frequently in primitive neuroectodermal tumors, particularly medulloblastoma, germ-cell tumors, ependymomas and malignant gliomas. It is estimated to occur in 2 to 3% of children with primary brain tumors. The incidence seems to depend on histology, as it rates 33% in malignant supratentorial gliomas and in anaplastic ependymomas. A review by Packer et al. disclosed an incidence of 19% in 314 consecutive patients, with half of them documented at first diagnosis and half during follow-up (Chamberlain et al.). Symptomatology does not differ from that observed in adults.

PERINEURAL SPREAD

Malignant cells can spread along the perineurium towards distant sites. This is a common occurrence, with intense symptomatology, in head and neck tumors progressing to the cranial cavity with ensuing leptomeningeal metastases.
Already observed in the middle of the 19th century (Cruveilhier), the phenomenon has been observed as neural metastases in almost all commonly occurring cancers. At the microscopic level, migration of malignant cells has been seen along the virtual space of the perineurium, not along perineural lymphatics as was first thought.
At present, the finding of a perineural spread in biopsies of any tumor, is widely seen as an unfavorable prognostic factor.

Two types of perineural spread occur. The first and most common is centripetal, where the cancer cells migrate towards the central nervous system, either the spinal cord or the brain. It is probably the main pathway for the leptomeningeal carcinomatosis. The other centrifugal, also called antegrade, has rarely been observed. In this form, the cells migrate towards the periphery. The latter results in subcutaneous metastases at the end of the nerves. We dare to suggest that retinoblastomas can metastasize to facial regions along the fibres of the trigeminal nerve. This is discussed in Part II.

Perineural Spread in Head and Neck Cancers

Perineural extension is a misleading clinical situation presenting as pain within the territory innervated by a sensitive nerve involved by perineural tumor spread from a skin or deeper lying tumor.
It is an uncommon situation but has been decribed and is encountered in skin cancers and tumors, mainly mucosal of the head and neck.
Perineural extension can be the route to more distant CNS involvement such as the cavernous sinus (Woodruff et al.), and the meninges, and even the intradural subarachnoidal space (see further Bourne).

Pathways and Clinics

Tumors lying in the region of the ophthalmic and maxillary division of the trigeminal nerve will spread to the orbit, but the orbital nerves will be the next affected. The site of entry is the infra-orbital canal. When the zygomaticofacial nerve is involved, the orbicularis oculi and/or the frontalis muscle will be affected.
More medially, it will follow the nasociliary and supraorbital nerve (fig.5.15). Laterally, it can follow the course of the zygomatic branch to the inferior orbital fissure.

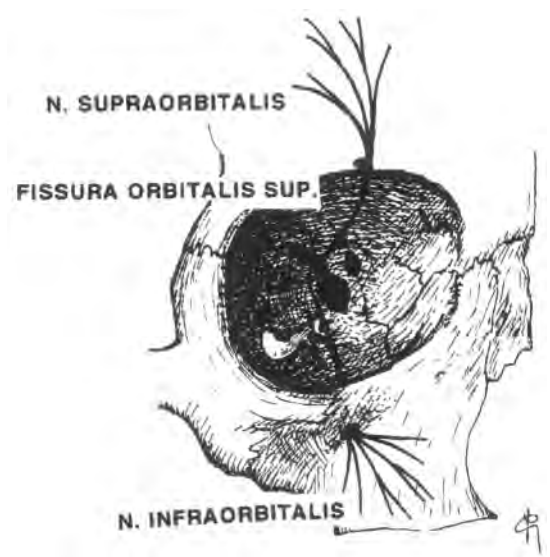

Fig. 5. 15 - Anatomy of the Periorbital and Orbital branches of the trigeminal nerve illustrating the possible intra-orbital perineural spread of facial tumors

The tumor cells follow the perineurium, but can break out at any point along the nerve, either within the orbit or within the further intrafacial or intracranial course (Clouston et al.). Such break-out will give rise to a mass lesion.

From the infraorbital nerve the cells can reach the fossa pterygopalatina, then to the inferior fissura and orbital apex, the infratemporal fossa and through the foramen rotundum to the middle cranial fossa. In cases of first involvement of the fifth nerve, progressive further involvement of the different branches of the facial nerve can be observed.
The involvement of the orbit will lead to the orbital apex syndrome and/or implication of the ocular muscles.

Table 5.72- Perineural Spread
Advantages of MRI and Signs Observed
Modified from Arcas et al.

Advantages
1. Greater contrast in soft tissue
2. Greater multiplanar capacity
3. No artefact from bone or dental device
4. Earlier ability to demonstrate muscular atrophy

Observed signs of perineural invasion
1. Concentric enlargement of the nerve
2. Appearance of a tumor in the lateral wall of the sinus cavernosus
3. Diffuse enhancement with adequate enhancement
4. Atrophy of muscles innervated by the affected nerve

Especially in cases of head and neck cancers, perineural spread causes intense pain, but also neurologic symptoms such as palsies, sensorial disturbances and secondary muscle atrophy as direct evidence. Indirect evidence is obtained by imaging methods. Modern methods, particularly MRI, have revolutionized the diagnostic possibilities so that it can now readily be recognized before symptomatology occurs (table 5.72).

Segmental enhancement on T1 sequences of the nerve is very suspect and replacement of the fat signal surrounding vessels or filling foramina and fissures will suggest perineural infiltration.
MRI is superior to CT for the evaluation of the pterygopalatine fissure, the orbital fissures and foramen ovale. MRI also provides a superior image of the cavernous sinuses and of Meckel's cave. Clinical examination, but also MRI for the deeper muscles, will eventually demonstrate muscular atrophy as indirect signs (Maroldi et al.).

Tumors with Perineural Spread

There is some correlation between the histology type and the frequency of perineural spread. Precise data are difficult to obtain, but it is very frequently observed in adenoid cystic cancers. Data for the incidence of perineural spread and squamous cell cancers were provided by Soo et al. in a series of 239 surgically treated patients (table 5.73). Overall, it was observed in nearly one third of the patients. The number of symptomatic patients was, however, not stated.
As far back as 1963, Ballantyne et al. reported on a large series of H&N cancer patients in whom perineural spread was observed (table 5.74). This concerned a pathology study of advanced cases and dates back to the pre-CT era. The relatively high number of skin cancers and the large variety of tumors implicated should be noticed. The low number of nasopharynx cancers is due to the fact that this site is almost never treated surgically. As we will discuss in the second part, perineural spread is frequent in this cancer.

Table 5. 73 - Perineural Spread
Incidence of Perineural Spread (N=239)
Data of Soo et al.

Site	N	Involved
Oral cavity (lip, tongue, floor, mucosa)	81	37.0%
Larynx	83	19.3
Oro - Hypopharynx	51	21.6
Nasal cavity, Sinuses	13	46.2
Other	11	9.1
Total	239	27.0

Table 5.74 - Perineural Spread
Primaries involved (N=80)
From the data of Ballantyne et al. (1963)

Skin	26	Parotid gland	8
Lip	17	Maxillary Sinus	4
Mucosa of cheek	3	Pyriform Sinus	2
Floor of mouth	5	Larynx	2
Gingiva	6	Mandibula	1
Tonsil	1	Submandibul.Gl.	2
Palate	1	Nasopharynx	1

Not all cranial nerves are implicated in the same proportion. This is probably due to an interplay between histology, the frequency of the tumors at each site and the anatomical characteristics of the cranial nerve.
In most adequately documented series, the trigeminal nerve is the most frequently cited, as most H&N tumors originate in the anatomical segment innervated by this nerve (Fig.5.16).

In several cancers such as those from the prostate, cranial nerve palsies can be first sign of an unknown cancer, mainly with a base of skull involvement.
In a series of 30 men presenting with a cranial palsy or neuropathy, the diagnosis of a systemic malignancy was not known in seven patients. In the 5 patients with multiple nerve involvement, it led to the diagnosis of bronchial cancer in 3, of renal cancer in 1 and of unknown primary of epidermoid histology.

The metastases were either intracerebral, meningeal or at the base of the skull. In the two patients with single nerve palsy, a bronchial cancer was involved, one with parasellar metastasis and in the other it could not be situated (Gupta et al.).

Leptomeningeal carcinomatosis is frequently manifested initially by dysfunction of one or more cranial nerves. Kan et al. have retrospectively reviewed patients observed with MRI where one or more cranial

nerves were enhanced without any other known cerebral or H&N pathology. They found seven patients in their files: two bronchial cancers, one rectal and 4 with lymphomatous disease. All patients except one had clinically multiple cranial nerve dysfunction. In 5 of these patients, the palsies were the first symptom of the primary disease, but the authors did not report which ones.

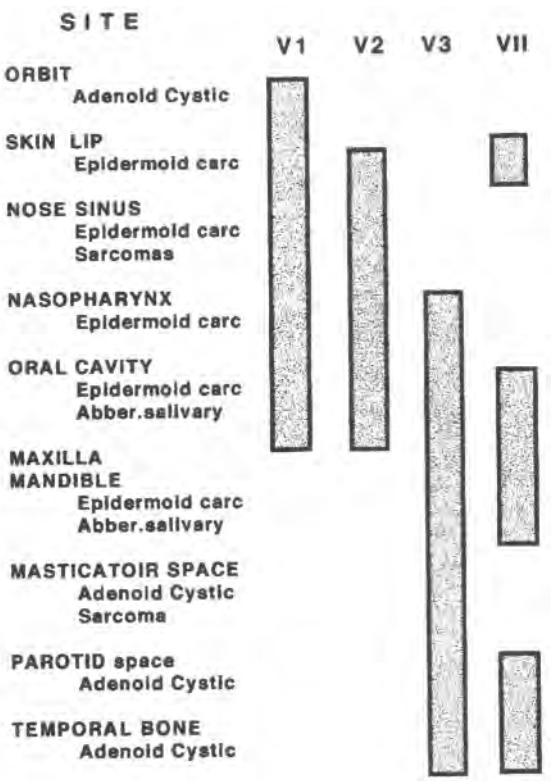

Fig.5.16 - Outline of the relationship between tumor site and cranial nerve involved (from data of Parker et al.)

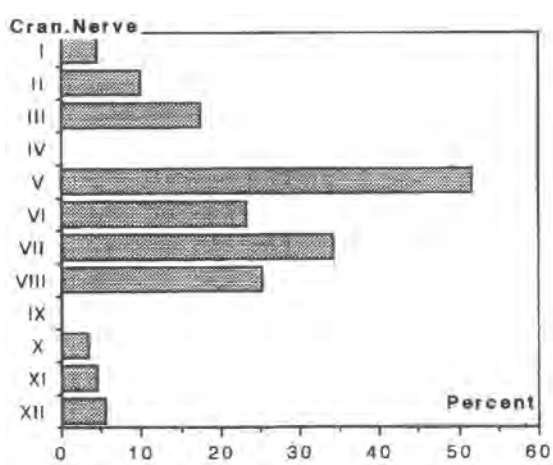

Fig.5.17- Distribution of cranial nerve involvement in 54 patients referred for radiotherapy because of invasion of the cranial base by different tumors (drawn from data of Schuster).

Schuster reported many years ago on a series of 54 patients undergoing palliative treatment for extensive destruction of the skull base. All had one or more cranial palsy, whose distribution is given in fig.5.17. The most frequently involved was the trigeminal, followed by the facial and the vestibular nerve. This should be compared with the graph concerning nasopharyngeal cancer (Part II, fig.13.6), where involvement of nervus VIII is almost absent.

MR Imaging features

Cranial nerve enhancement on MRI is the mainstay of the diagnosis. The enhancement is usually located at the cisternal and intracanalicular portions, while for the optic nerve it is commonly seen at the peripheral portion (Kan et al.).
Some associated features can be noted and are indicative fof a malignant process:

- superficial and/or periventricular brain metastasis, indicating pial and subependymal invasion;
- pial subarachnoidal enhancement;
- pachymeningeal enhancement;
- muscle atrophy.

METASTASES to PERIPHERAL NERVE, PLEXUS and DORSAL ROOT GANGLIA

Metastatic infiltration of peripheral nerves is probably much more frequent than usually accepted, but is most often misdiagnosed as a non-oncological problem or even as a sequella of previous treatment, radiation therapy being incriminated if it had been administrated.
Nevertheless the involvement of nerves is not so rare and differential diagnosis with radiation sequella is frequently possible.

True neural metastases are rarely reported. Reporting on one patient, Cantone et al. found only six reports involving peripheral nerves. In all, metastatic melanoma was concerned.

Data on the incidence are not available, except an approximation from Saphner et al. They reviewed 2,261 records of patients with cervical carcinoma. They found 50 cases of lumbosacral plexopathy, and, after subtracting the 1,042 patients with carcinoma in situ, the result represents an incidence of 4.7%. The data should have been related to stage and follow-up time.

Pathways

In general, four causes can be documented of an oncologic plexopathy. The most frequent had metastatic involvement and radiation sequellae (Pettigrew et al., table 5.75).
Involvement of the cervical plexus implies a close proximity of the tumor to the spine. Epidural com-

pression at level C1-C4 may result in life-threatening respiratory paralysis (nervus phrenicus) (Jaeckle).
The brachial plexus (fig.5.18) is usually invaded by contiguous tumors. The lateral group of the axillary lymph nodes is in close contact with the divisions of the lower trunk of the plexus. Lymph nodes are rarely neighbouring the upper trunk (Kori et al.). When the lower trunk or the medial cord is affected, it gives rise to weakness of intrinsic hand and wrist muscles with sensory loss in the C8-T1 distribution. This is at variance of the conclusions of Harper et al. in respect of 90 patients, where no anatomical difference between the two groups was found.

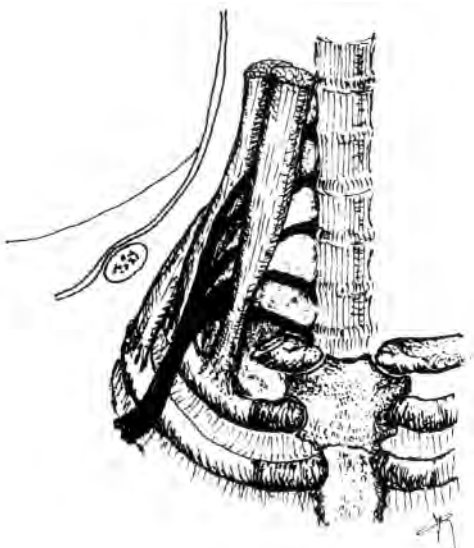

Fig. 5.18 - Topographic anatomy of the plexus brachialis showing its relationship with the different scalenus muscles.

Table 5. 75 - Oncological Causes of Plexopathy
Modified from Pettigrew et al.

1. Metastatic involvement
   a. true neural metastases
   b. infiltration from neighbouring tumor or recurrence
2. Radiation induced plexopathy, dose dependent
3. Sequellar to intraarterial chemotherapy
4. A second tumor (very rare)

The lumbar nerve plexus is found within the psoas muscle. The different nerves originating from the plexus innervate the inguinal zone, and the thigh up to the knee. The sacral plexus is situated at the ventral sur-face of the m.piriformis within the pelvic wall and it innervates the gluteal, the posterior thigh and lateral aspects of the perineum. The different cutaneous zones will be concerned with irradiating pain and sensory loss occuring.
Metastatic lumbosacral plexopathy usually results from direct extension from pelvic neoplasms or from metastatic regional lymph nodes, sacrum, iliacal, or carcinomas of the colon, the rectum, gynecologic malignancies and retroperitoneal sarcomas. In 15%, it is even the first presentation of a malignancy (Jaeckle). The incidence of the lumbar and other plexopathies is unknown, in the first place because it is a difficult diagnosis, mainly occurring in advanced cancers, and also because the diagnosis is probably labelled as cancerous invasion and recurrence, without further investigations.
Interesting data have been provided by Saphner et al. They compared the symptoms at presentation and during the course of the disease (table 5.76).

Table 5. 76- Lumbosacral Plexopathy
Neurologic Symptoms
Data of Saphner et al.

Symptoms (N=50)	Diagnosis	Evolution
Pain	96%	100%
Weakness	10	50
Numbness / Paresthesias	10	32
Incontinence	0	8
Signs		
Sensory	84	86
Motor	59	67
Reflexes	38	51
Spincter flaccidity	5	5

Pathology

Three direct structural anatomic pathways allowing tumorous infiltration that can lead to functional disturbance have been described(Meller et al.).
1. the tumor can stretch the nerve trunk by pushing it without invading the sheath;
2. the mass can compress or strangulate the nerve trunk by engulfing it, without there being genuine invasion of the sheath;
3. the tumor can perforate the nerve sheath directly and invade it between the fascicles. The latter is then described as perineural or neural invasion, along whose routes the tumor can spread into a neighbouring structure.

Involved Primaries

Of 41 patients reported by Kori et al., bronchial (14) and breast cancer (13) were the majority of the primaries involved in metastatic brachial plexopathy. Four infra-diaphragmatic tumors and 4 of unknown primaries were the other. They probably had supraclavicular metastases (see further).
In a series of 30 cases from the MD.Anderson Hospital, Ampil et al. were able to distinguish 25 cases of rather contiguous invasion from recurrent pelvic tumors as rectal (18) cervical (4) and prostatic cancers (3). The 5 others could be regarded as purely metastatic, with one breast cancer, two bronchial cancers (oatcell and squamous cell), one Hodgkin and one myeloma.

Symptomatology / Differential Diagnosis

This topic has been addressed by Kori et al. for the

brachial plexus. They compared metastatic cases with radiation plexitis, a not uncommon situation in oncology patients (table 5.77).
Metastatic brachial plexopathy presents more frequently with pain and Horner's syndrome, and is almost exclusively located in the lower part of the plexus.

Table 5. 77 - Metastases to the Brachial Plexus
Symptomatology compared with radiation plexitis
Modified from data of Kori et al.(1981)

Symptom	Metastases(') N=44	Radiation N=22
Pain	75%	18%
Dysesthesia	25	55
Weakness	0	27
Horner syndrome	53	14
Lymphedema	13	73
Anatomical Site		
Trunk C5-C6	0	77
Trunk C8-T1	75	0
Whole C5-T1	25	23

(') omitting the group of metastatic plexopathy previously irradiated.

A number of important differences can be distinguished in the symptomatology of both groups (Harper et al.):
1. Patients with neoplastic plexopathy have higher frequency of pain as initial and predominant symptom;
2. They have a shorter duration of symptoms prior to diagnosis of plexopathy;
3. There is a higher incidence of Horner's syndrome;
4. At CT, in tumoral plexopathy, there is always a discrete or pronounced mass visible involving the plexus.

Metastatic lumbosacral plexopathy is usually unilateral, with only 25% of cases being affected bilaterally. The tumoral plexopathy is installed either by direct extension, though the pathway for extrapelvic tumors is most probably a hematogenous one. The tumors do not always involve the plexus at the exact level of the organ of origin and distant areas of the plexus are apparently involved from metastatic lymph nodes, bones or soft tissue (Jaeckle).
The responsible tumors in the large series from Jaeckle are on table 5.78. Pelvic tumors accounted for 45%; when retroperitoneal (kidney) and lymphoma are added, 57%. Direct invasion of plexus was noted in 73% and by metastases from extra-abdominal tumor in 27%.

Pain is the initial symptom of lumbosacral plexopathy, followed in the weeks or months thereafter with progressive numbness of the leg and weakness. The pain is described as dull, aching or boring. It is often worsened by lying supine. Sometimes it is aggravated by bowel movement or urination. The pain type can be local, referred or radicular (table 5.79).

Table 5.78 - Cancerous Lumbar Plexopathy
Involved Primaries (N=85)
Data of Jaeckle 1985

Pelvic Tumors		Extra Pelvic Tumors	
Colon rectum	17	Breast	9
Cervix Uteri	6	Kidney	3
Urin.Bladder	3	Bronchus	3
Uterus	3	Stomach	2
Testes	3	Thyroid	1
Ovary	3	Undefined	
Prostate	2	Sarcoma	14
Ureter	1	Lymphoma	8
		Melanoma	4
		Neurofibrosarc	1
		Mal..Schwannoma	1
		Unknown	1

Table 5. 79- Malignant Lumbar Plexopathy
Early Symptomatology vs. Follow-Up (N=85)
Data of Jaeckle 1985

Symptom	At Presentation	Later
Pain	91%	98%
Numbness	18	42
Weakness	15	60
Paresthesias	13	33
Incontinence	5	9
Impotence(')	11	11

(') Men only

The dominance of pain in the clinical presentation is stressed by Thomas et al. It is the first symptom in almost all patients with tumoral plexopathy and principally affects the proximal areas such as low back, buttock, hip and thigh. Additionally, weakness accompanies the pain. Unlike with radiation plexopathy, the weakness will be overridingly unilateral, though it can be proximal, distal or diffuse.
The symptomatology at presentation is clinically the most important for early diagnosis and must be compared with the symptomatology during further course 'at installation' (table 5.80). The absence of pain with neurological symptoms such as numbness, present in 40%, and weakness, present in 60%, should raise suspicion for leptomeningeal carcinomatosis.

Paresthesia with burning sensation,also described as 'hot foot', is present in about one third of the patients (Jaeckle).
Positive reverse straight leg raising, as well as relief of pain with high-dosage steroids, is according to Pettigrew et al., strongly indicative of plexopathy secondary to tumor.

Jaeckle has also distinguished three anatomic levels of involvement: the upper (L1-L4), the lower (L5-S3) and the pan-plexopathy (L1-S3). The differentiation in symptomatology is outlined in Table 5.81

Within the three syndromes, three other specific syndromes have been individualized.
- Only paresthesias in the lower abdominal or groin,

with the tumor on CT next to L1;
- Lumbosacral trunk syndrome with numbness over the dorsomedial foot and sole with weakness of knee flexion, ankle dorsiflexion and inversion. The tumors were eroding the sacral ala;
- Coccygeal involvement (rectal tumors) with perineal sensory loss and sphincter weakness.

Table 5. 80- Metastases to the Lumbosacral Plexus
Symptomatology
Modified from Jaeckle, 1985-1991

Leg Weakness	86%
Sensory Loss	73%
Focal Reflex Loss	64%
Focal Tenderness	55%
with Direct SLRT (')	53%
Leg edema at involved side	47%
with reverse SLRT	45%
Dysesthesia	15%
Rectal Mass	39%
Decreased Sphincter Tone	12%

Separate syndrome L1-L4 upper plexus
L4-L5 lumbosacral trunk
S1-S4 lower plexus
Possible in cervix uteri or rectal cancer:
numbness and dysesthesia in perineum
(') Straight Leg Raising Test

Diagnosis

A thorough neurologic examination is of the utmost importance. The quintet of leg pain, weakness, edema, rectal mass and hydronephrosis is highly suggestive of lumbar plexopathy (Jaeckle). EMG certainly has a role.
Myelography can demonstrate epidural deposits confirming the metastatic nature and explaining the symptomatology, if the clinical finding suggests a central disease. When the disease seems peripheral, CT, or now MRI, is indicated (Armington et al.).

Clinical symptoms can raise suspicion of an infiltration of the brachial plexus. MRI is presently the imaging method of choice. According to DeVerdier et al. who studied 16 cases, pathological lesions are best appreciated on T1W and T2W images in all cases. The images in the coronal plane are particularly useful.
CT is very important for delineating lumbar and/or pelvic pathology, as lymph nodes, recurrent tumors or true metastases in the prevertebral or pelvic area. CT should in fact be the first to delineate the anatomy of the tumoral invasion of the lumbar plexus. EMG is helpful in the cases of radiation plexopathy, as more than half of the patients showed 'myokymic' discharges. This was confirmed by Harper et al, but the test has no absolute value.
A CT-guide fine needle biopsy can be undertaken, when the diagnosis is not obvious.

Differential Diagnosis

The presence of saddle anesthesia or loss of bladder and anal sphincter control allow a distinction between lesions of the conus medullaris within the spinal cord and those of the cauda equina or lumbo-sacral nerve plexus. Pain is the dominant sign in plexopathy, while it is rarely present in cord compression.

Metastases in the Dorsal Root Ganglia

At autopsy; lumbar spinal ganglia were the site of metastatic carcinoma in 10 of the 200 patients, or 5% of the patients who had also central nervous metastases of any kind and in 2 other patients without CNS metastases (Chason). They were the first reported cases in the literature, but the primaries were not mentioned. Subsequently two other cases were reported, also in the lumbar ganglia (Johnson), one from a colonic carcinoma and one small cell bronchial cancer.

Table 5.81 - Malignant Lumbar Plexopathy
Differentiation according to Level of Involvement
Prospective study by Jaeckle in 34 patients

	Clinical Level		
	Upper Plexopathy	Lower Plexopathy	Pan-Plexopathy
Characteristics	N=12	N=16	N=6
Most Common Tumor	Colorectal	Sarcoma	GenitoUrinary
Pain Local	Lower Abdomen	Buttock, Perineum	Lumbosacral
Radicular	Anterior Thigh	Posterolateral thigh, leg	Variable
Referred	Flank, Iliac Crest	Hip and ankle	Variable
Numbness - Paresthesias	Anterior Thigh	Perineum, thigh, sole	Anterior thigh, leg, foot
Motor - Reflex Changes	L2-L4	L5-S1	L2-S2
Sensory Loss	Anterolateral Thigh	Posterior Thigh, Sole	Esp. anterior Thigh, Leg
Tenderness	Lumbar	Sciatic notch, Sacrum	Lumbosacral
Positive SLRT (')direct	6/12	8/16	5/6
reverse	2/12	8/16	5/6
Leg Edema	5/12	6/16	5/6
Rectal Mass	3/12	7/16	1/6
Sphincter Weakness	none	8/16	none

(') SLRT: Straight leg raising test

METASTASES to the PITUITARY GLAND

Metastases in the pituitary gland are a relative frequent problem in oncology patients, especially in breast cancer patients. At autopsy, many more are found than was suspected in vivo and were asymptomatic. It is possible, however, that deterioration of the patients' condition had masked their presence, so that they were neither recognized, nor sought for.

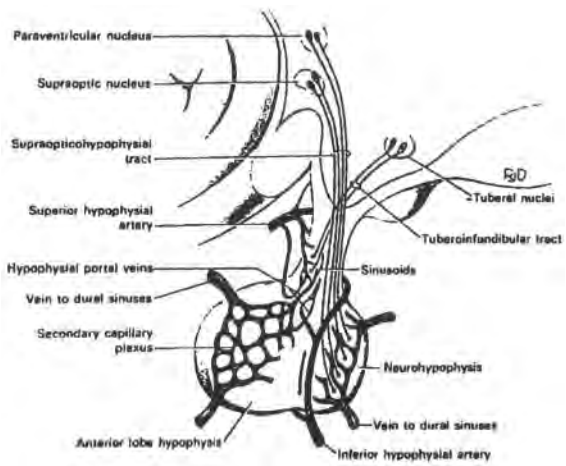

Fig.5.19 - Vascular anatomy of the hypothalamic-pituitary axis. The superior hypophyseal artery goes up in a capillary plexus and hyphyseal portal veins. The portal system ends in a second capillary plexus (From Chong et al., with permission)

Pathways

Except for those cases where a neighbouring tumor invades the sella, such as happens with nasopharyngeal cancer, all are hematogenic.
The arterial circulation provides a direct vascularisation of the posterior gland, whereas the anterior lobe is 'protected' by its portal system. This probably explains why the posterior lobe is the most frequently involved (Fig.5.19).

Incidence

In a large autoptic series of 1000 oncology patients, Schneider et al. found 40 patients with a pituitary metastasis. As can be observed from table 5.82, the highest frequency is observed in breast cancer patients.

A large transsphenoidal surgical series of 911 cases, found 83 non-pituitary masses of whom 12 were metastatic disease. It was the only metastatic focus in one patient (Freda et al.).

Primaries Involved

Several small series have been reported. We could only find data according to gender in the series from Teears et al. dealing with 88 patients (table 5.83). The majority concerns breast cancer in women and bronchial cancers in men. In the recent literature, several cases of thyroid and renal cancers, even as type 1 presentation, have been reported.

Table 5. 82 - Metastases to the Pituitary
Autopsy data according to Primary (N=1000)
Data of Schneider et al. 1972

Primary(')	Naut.	N with pit.met	%
Breast	73	14	19.2%
Bronchus	182	14	7.7
Stomach	163	3	1.8
Colon	100	2	2.0
Bile Duct	83	1	1.2
Kidney	40	1	2.5
Prostate	35	1	2.9
Various	122	2	1.6

(') the other cancers had no pituitary metastasis

Table 5.83 - Metastases to the Pituitary
Primary Tumors Involved (N=88)
Data of Teears et al. 1975

Women (N= 53)		Men (N=35)	
Breast	35 (66%)	Bronchus	22 (63%)
Bronchus	7 (13%)	Prostate	3 (8%)
Stomach	4	Urin.Bladder	2
Head Neck	3	Head Neck	3
Endometrium	1	Ileum	1
Ovary	1	Pancreas	1
Cervix Uteri	1	Skin	1
Colon	1	Unknown	1
		Penis	1

There is a clear discordance between the reported clinical cases and the relatively high incidence in autopsy series dealing with particular primaries.
A particularly rare site for metastases is the region englobing the pituitary-hypothalamic axis. They should, in fact be considered diencephalic cerebral metastases, but as their symptomatology is very similar to the pituitary metastases, we will mention them here.
Schubiger et al. have reported on a series of 7 symptomatic patients, of whom five had diabetes insipidus and two a clear hypohormonal syndrome. Four patients were breast cancer patients, while two had a bronchial tumor, one a stomachal and one had myelogenous leukemia. All patients had multiple other metastases. At MRI the tumor was either suprasellar or 4 other patiients intra and suprasellar.

Pathology

The site of the metastases within the sella or/and the pituitary is a matter of discussion in the literature and has yielded conflicting results. We cannot comment on the subject, and merely cite some data here.
In a series of 88 autopsy cases, Teears et al. noted a slight predominance in the posterior lobe (table 5.84). A differentiation according to primary was not made, neither on relation with site within the pituitary.

Table 5. 84 - Metastases to the Pituitary
Location of the metastases (N=88)
Data of Teears et al. 1975

Posterior lobe	30 (56.8%)
Anterior lobe	12 (13.6%)
Anterior and posterior	11 (12.5%)
Capsule	11 (12.5%)
Stalk	2 (2.3%)
Capsule and Stalk	2 (2.3%)

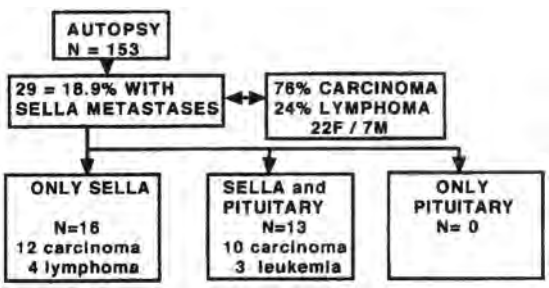

Fig.5.20 - Pathology of the sella in 29 patients with sellar metastases (drawn from data of Saeger et al.)

Other data were provided by Schneider et al. and Max et al. and showed almost the same distribution.
However, different results were obtained in an autopsy study of 153 oncology-patients which yielded 29 patients with 'sella-metastases' or 18.9%. The authors described 16 cases where only bony sellar metastases were found and 13 where the metastases involved both bone and pituitary. The pituitary was never invaded alone (Saeger et al.) (fig.5.20).
On inspection, pituitary metastasis is rarely visible, and must be examined at microscopy. Mul-tiple foci are frequently seen (fig.5.21).
Reviewing 280 autopsied oncology patients, Delarue et al. found a higher proportion of adrenal meta-stases in patients with hypophyseal metastases.

Symptomatology

The most frequent sign of pituitary metastases will be a diabetes insipidus, but this does not always point to a metastasis (see further).
In many patients, the presentation of a pituitary symptomatology is the first manifestation of an unknown tumor. In a series of 14 patients, only 5 had a known tumor (Branch et al.). While diabetes insipidus is a cardinal symptom in oncology patients, not all pituitary metastases present with DI. Branch et al. have drawn attention to particular presentations:
- one women with galactorrhea and amenorrhea;
- anterior hypopituitarism, such as hypoadrenalism, hypothyroidism or hypogonadism were the symptoms in 9 patients either in combination or alone;
- visual deficit or ophtalmoplegia alone.

In their series 10 of the 14 complained of headache.

Metastases to the pituitary are not particularly rare in oncology and must be differentiated from a primary pituitary adenoma. When the patient presents first with an unknown or unreported diagnosis of breast cancer this can be rather difficult. According to Aaberg et al. pituitary metastases are accompanied by oculomotor palsy in 45%, by headache in 61%, and a diminished visual acuity in 35%. These symptoms are almost absent in pituitary adenomas. The possibility of metastases is likely when there is a rapid onset and progression in person aged above 50 years, presenting with cranial palsies and diabetes insipidus.

In many patients, however, pituitary metastases are part of a widely disseminated metastatic process.
The presenting symptoms and signs are shown in table 5.85.

Table 5.85 - Metastases to the Pituitary
Signs and Symptoms in 36 patients
Data of Morita et al. 1998

Symptom	
Diabetes Insipidus	22 (61%)
Retroorbital pain / headache	17 (48%)
Visual field deficit	12 (33%)
Fatigue	11
Nausea /Anorexia /Vomiting	3
Signs	
Anter. hypopituitarism	17 (48%)
Panhypopituitarism	8
Ophtalmoplegia	9
Cognitive deficit	4
Facial Numbness	2

One case has been reported of a pituitary metastases from a colonic cancer, secreting prolactin, leading first to the diagnosis of a prolactinoma (Leramo et al.).

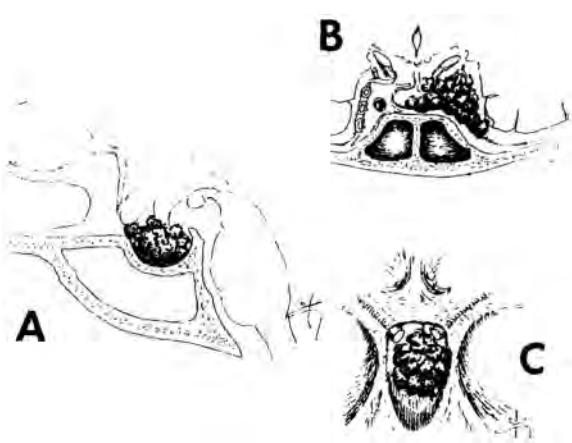

Fig.5.21 - Different views of a metastasis to the pituitary gland (A) lateral view; (B) frontal view; (C) cranial view.

Diagnosis Imaging

While clinical suspicion and laboratory studies are important, imaging with CT or (better) with MRI is the clue to diagnosis. The imaging findings in 36

cases were reported by Morita et al. (table 5.86). Imaging studies are not specific, but the presence of extensive bone destruction is helpful for diagnosis. Some authors state that there is always bone destruction. In the 14 patients discussed by Branch et al., the enlarged sella extended suprasellarly, laterally or was accompanied by a mass.
The combination of age over 50yrs, cranial nerve abnormalities, diabetes insipidus and a rapidity progressive mass should rise the suspicion of a metastatic process within the sella (Freda et al.).

Table 5.86 - Metastases to the Pituitary
Imaging features in 36 patients
Data of Morita et al. 1998

Homogenous enhancing sellar mass	22 (61%)
Suprasellar enhancing mass	14
Stalk enhancement - enlargement	11
Invasion of Cavernous sinus	7
Mass in Sphenoid sinus	3
Invasion of Hypothalamus - Optic nerve	2
Other sellar abnormality	4
Negative images	1
Other brain lesions present	3

Differential Diagnosis

Not every diabetes insipidus is a specific symptom of pituitary metastases. Of 100 consecutive patients with this complaint, only 14 were caused by a metastatic tumor, as many as from primary tumors of that region (table 5.87).

Table 5. 87 - Diabetes Insipidus
Etiology in 100 Consecutive Patients
Data of Kimmel et al. 1983

Idiopathic	25
Secondary	
Trauma (accidental, surgery)	27
Primary Intracranial Tumors	13
Metastases in the Pituitary	14
Vascular Disease	1
Infectious Disease	2
Systemic Diseases	9
(Histiocytosis, Sarcoid, Granuloma, sickle cell , etc.)	
Empty sella syndrome	1

Table 5.88 - Pituitary Metastases vs.Adenoma
Comparative Features
From Aaberg et al.

Symptom	Metastases MacCormick	Adenoma Aaberg	Hollenhorst
Diabetes Insipidus	70%	33%	1%
Visual Loss	20%	61%	70%
Palsies	12%	42% Diplopia	0.8%
Hypopituitarism	18%	53% Palsies	4.6%
Headache	--	61%	--
Dimin.Vis.Acuity	0%	33%	--

Other symptoms to be differentiated are chiasmal syndrome and ophtalmoplegia.

A pertinent review on the subject was provided by Aaberg et al. They compared the symptomatology of pituitary metastases with that of adenoma (table 5.88).

Overall Conclusion

Summarizing, it can be concluded that bronchial cancer is the most frequent primary metastasizing to the most important parts of the CNS. Breast cancer, however, is certainly also a frequent intruder.

Metastatic SITE	Primary Most Frequently Involved
Cerebral Hemisphere	Bronchus (all histol)
Choroid Plexus	Bronchus (all histol)
Pineal gland	Bronchus (all histol)
Cerebellum	Bronchus (all histol)
brain stem	Bronchus (all histol)
Intramedullary	Bronchus (all histol)
Meningeal Carcinomat.	Breast Cancer in women Bronchial cancer in men

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Caution: References are given for documentary purposes. Not all have been reviewed or used in the redaction of the text. We do not claim completeness of data. The references are as much as possible grouped per subject heading.

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6

METASTASES to the HEAD and NECK

The term 'Head and Neck' in oncology refers to the entire volume beneath the skull base and including mostly the upper respiratory and digestive tract, in effect nose and sinuses and the oral cavity. For practical reasons, in this chapter we will also include ophthalmic metastases and metastases in the salivary glands. The metastases to the thyroid and parathyroid glands are also discussed in this chapter.

The whole region is highly vascularized and surprisingly relatively rarely involved in metastatic processes compared to other regions. The symptomatology is, however, frequently obvious and distressing, due to the important social and feeding function of the face and facial massive.

For patients with a known tumor, this region will always be a suspect area, but the diagnosis will be rather difficult in case of type 1 metastases, even though such metastases are not particularly rare in this region. Many tumors may well be revealed by a signal in that region, even from below the diaphragm.

Metastases within this region are much less frequent than primaries. They will have to be differentiated from second primaries, a common occurrence within this region, especially in patients with bron-chial cancer. This points to the heavy responsibility of the pathologist when H&N biopsies are submitted.

METASTASES to the SALIVARY GLANDS

Metastases in the salivary glands are a rare event. The literature, however, is somewhat confusing as it usually mixes two types of metastases, at least in the parotid gland.

METASTASES to the PAROTID GLAND

Pathways

Metastatic cells can reach the parotid gland via two paths, leading to two different types of metastases.

The parotid gland encloses a rich network of lymphatics and lymph nodes that are tributaries to the skin and mucosa of the oral and nasal cavity. Such a situation gives rise to the first type of parotid metastases; the involvement of the intra-parotid lymph nodes by metastatic cells from tumors of the skin or of the mucosa. This was first described by Conley et al. (fig.6.1).

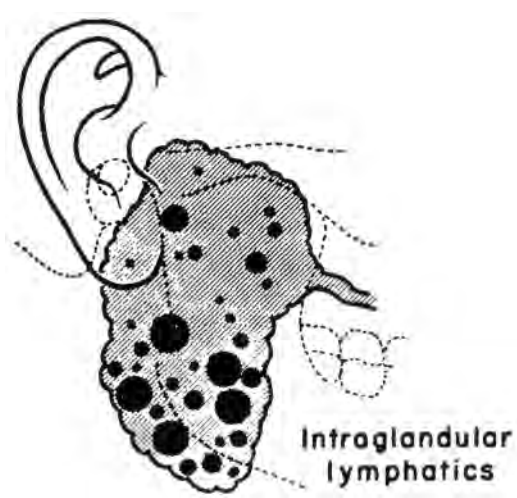

Fig.6.1 - The lymphatics and lymph nodes within the parotid gland. (From Conley et al., with permission)

They form a functional unit with the extra or para-parotid lymph glands, which are much more frequently occupied by metastatic cells. They can however perplex the pathologist. Batsakis states that unless the lymph node has been overrun, identification of its capsule and a clear delineation from the parotid parenchyma the diagnosis of intraglandular lymph node metastases will be possible.
The parotid node also drains the skin of a large part of the head (cranium and face), but also the mucosa of the sinus (fig.6.2).

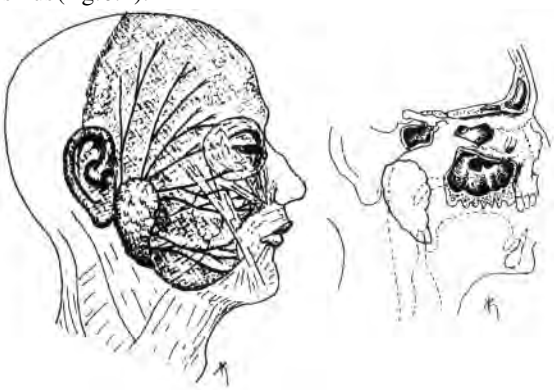

Fig. 6.2 - The parotid nodes drain the skin of the lateral half of the face and also the sinusal cavities.

The second metastatic pathway is hematogenous, and results in intra-parenchymal metastases, mostly from infraclavicular neoplasms.

In the files of one institute, Rees et al. found in 545 patients with a malignant parotid tumors, 52 patients (9%) with a secondary parotid tumor. They did not, however, distinguish between the two types of metastases, as they included 31 squamous skin tu-mors and 7 skin melanomas.

Reviewing 75 metastatic cases in the parotid taken from the German Salivary Gland Tumor Register, Seifert et al, were able to divide them in 37 parenchymal and 38 lymphatic metastases (table 6.1). It would seem that both types have the same frequency. The Register had collected 10,944 tumors of all salivary glands, so that with 108 cases, the incidence of metastases is only 1/1000.

Table 6.1 - Metastases to the Parotid Gland
Types and Primaries
from Register Data by Seifert et al., 1986

Primary	Parenchymal	Lymphatic
Skin, squam.ous cell	12	11
Skin, melanoma	6	9
Nasopharynx	2	7
Thyroid	1	1
Bronchial cancer	5	--
Kidney	4	--
Breast	2	--
Unknown Primary	5	10

A distinction between the two types is not always made in the few reports there are.

Primaries

As shown in table 6.1, skin cancer and melanoma are the main sources of metastases.
Up to 1984, there were 23 case-reports from metastases in the parotid from infraclavicular tumors. They consisted mainly of bronchial, renal and mammary cancers. Since then, of course, many more have been reported, even from cerebral tumors. The most recent review is from Pisani et al. in 1998, reviewing 866 cases, though a distinction between lymph node metastases and intra-parenchymal was not made. It is, however, obvious that all infraclavicular tumors resulted in parenchymal metastases (table 6.2).
The cases are sometimes difficult to retrieve as they are reported in series of malignant tumors, together with the primaries.

A metastasis within the accessory parotid gland, from a prostate cancer was reported by Goldberg et al. in a 77-year old man. There were a few other bone and skull metastases.

Table 6.2 - Metastases to the Parotid Gland
Primaries, cases from 1965-1994 (N=866)
Literature Review by Pisani et al. 1998

Site			
Skin, squam.cell	313		
Skin, basal cell	25		
Skin, Melanoma	336		
Supraclavicular		**Infraclavicular**	
Nasopharynx	25	Kidney	33
Oral cav.+ oroph.	28	Bronchus	25
Larynx, hypoph.	4	Breast	15
Nose / Sinuses	7	Colon rectum	6
Thyroid	6	Prostate	8
Cerebral	2	Stomach	2
Orbit	10	Other	3
Unknown Primary	12		

Reporting on 36 cases of secondaries in the salivary glands, Zhang et al. noted 12 lymphomatous tumors, 10 skin melanomas, 2 facial sarcomas, 6 facial skin cancers and only 3 distant tumors (2 bronchial and one from the breast).

Type 1 Presentation

There are several reports where the parotid 'tumor' was the first sign of an infraclavicular tumor. This is a common feature in renal cancer.

Symptoms

The main presentation is a tumefaction, usually fast-growing, but pain is also frequently present.

Diagnosis

When the patient is known to have been treated, any such symptom must be regarded as suspicious, especially when the tumefaction is recent and fast-growing. Fine needle aspiration cytology or biopsy may indicate the primary. Excision biopsy can be locally curative in case of solitary metastases.

METASTASES to the SUBMANDIBULAR GLAND

Metastases in the submandibular gland are much rarer than in the parotid. A number of authors have stated that there are no lymph nodes within it (Vaidya et al.), though Seifert actually could discern between the two metastatic types (table 6.3).

Table 6.3 - Metastases to the Submandibular Gland Types and Primaries from Register Data by Seifert et al., 1986

Primary	Parenchymal	Lymphatic
Skin, squam. cell	2	7
Skin, melanoma	--	2
Nasopharynx	--	4
Thyroid	--	1
Bronchial cancers	2	--
Kidney	2	--
Breast	3	1
Rectocolon	1	--
Cervix Uteri	--	1
Unknown Primary	--	7
TOTAL	10	23

In the period up to 1986, Seifert et al. found 8 other metastatic cases in the literature: 3 from a bronchial cancer, 2 from a renal and 3 breast cancers. We have found a number of other references since then, also mainly renal and mammary cancer.
One type 1 presentation from a renal cell carcinoma was reported by Bedrosian et al., and one from a cecal carcinoma was reported by Legros et al.
A submandibular swelling in a 45 year old man turned out to be a first sign and metastasis of a small cell cancer (Brodsky et al.). The latter reviewed the literature at that time and found only 5 other cases reported (1 bronchial, 2 breast and 2 'head and neck').

We are not aware of any cases which are metastatic to the sublingual gland.

OPHTHALMIC METASTASES

In ophthalmic metastases, a distinction has to be made between the different sites within the orbit and the eye.

These different sites have their own incidence rates and symptomatology. The most frequent are certainly those within the choroid.

HISTORY

The first report in the medical literature concerning metastases to the orbital region was from Horner, the well-known pathologist in 1864. In 1872, Perl reported an autopsy study of a patient with breast cancer and demonstrated the presence of choroidal metastasis. Wintersteiner made a diagnosis of muscular metastases in the orbit, as far back as 1889.
In 1907, Axenfeld presented at the German Society of Ophthalmology with a case of metastatic breast cancer to the orbit. In 1923 Usher contributed a valuable review of the up to then 110 reported cases of metastatic carcinoma in the eye.

In 1953, Gronwall published the first case of a metastatic eyelid carcinoma.

As vision problems or loss of sight are a severe threat to the patients' quality of life, and indeed also to that of his environment, any 'ocular' complaint should be taken seriously, investigated properly and adequate treatment instituted promptly.
We would mention that the same problem can also occur in men with breast cancer, in spite of its low incidence.

Many authors have stressed that the eye and the orbit are not infrequently involved in the clinical pathology of breast cancer. In 1950, Willis remarked that of his 140 autopsy cases with eye involvement, 78 were breast cancer patients.

CHRONOLOGY
The patient can present with 'metastatic complaints' at different phases in the evolution of a cancer pathology.
It only rarely occurs that examination of the metastases reveals the primary, where a breast or other cancer is found by further examination of the patient. Raymond found that between 12 and 30% of the ocular metastases were the first instance in the evolution of breast cancer and in 6% of the patients of Beati et al. ophthalmologic metastases were the first sign of an unsuspected breast carcinoma. In various reports, quite a number of these ophthalmic metastases are the first event of a metastatic progression.
Ratanatharatorn found 22% of their 32 patients presented at the first recognition of disseminated cancer. In the large series of 420 uveal metastases, Shields et al. found a 30% with uveal metastases as first presentation. It is striking that in about half of them the primary was not found or at least was asymptomatic.
The metastases can be present simultaneously with the primary and be found during the staging procedures after diagnosis of the primary tumour, but the large majority of the metastases occur after months or

years, even decades.
They also remarked that in 90% of the patients who developed eye metastases, it was discovered in the last quarter of their life, indicating the dismal prognosis of this diagnosis.
In a prospective study, Mewis disclosed choroidal metastases during the follow-up in 10 to 35% of breast cancer patients.
During the course of 420 patients evaluation for their complaints, 70% were found to have metastases elsewhere. For 20%, the first systemic metastasis was in the lung. For the other sites the percentages were lower (fig.6.3).

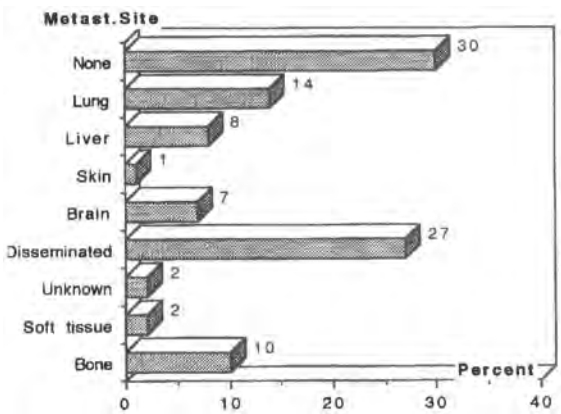

Fig 6.3 - Initial systemic metastatic site before the diagnosis of uveal metastases (N=420). Redrawn from Shields et al.

If the patient does not report any previous treatment for (breast) cancer to the ophthalmologist, valuable time may be lost.
As can be seen from fig.6.3, the metastases are the first sign of metastatic disease in thirty percent of patients with uveal metastases.

Incidence / Prevalence

The real incidence of such metastases being unknown, some have tried to evaluate their incidence.
According to the survey by Orenstein et al. based on the ratio of such cases to all other cases of metastases admitted to ophthalmic hospitals the frequency ranges from 1:147.000 to 1/35.000. It would be very interesting to evaluate the number of ophthalmic metastases according to the total number of patients with malignant disease. Albert et al. have pointed out that in institutions where a large number of patients are treated, one would expect the percentage of metastatic disease to the eye to be larger. They found that for 190 malignant tumors of the eye, orbit and adnexae at the University of Pennsylvania, between 1950 and 1965, nearly 25% were of metastatic origin.
In 10,592 breast cancer patients between 1947 and 1972, Thatcher et al. calculated an incidence of 0.4%. This is probably an underestimation.
Gross ocular metastases in patients dying from cancer were seen in about 5% of the cases in the autopsy series at the Johns Hopkins Hospital (Eliassi-Rad et al., table 6.4). We would point out that only 36 breast cancers are included, none of which had gross metastasis, although at microscopy 8.3% were found with metastases.

Table 6.4 - Ocular Metastases at Autopsy Data in 741 patients, Eliassi-Rad et al.1996

	Gross	Microsc.
Leukemia	13.0%	no data
Lymphoma	6.7	no data
Myeloma	22.6	no data
Sarcoma	4.0	no data
Oropharynx	4.8	5.0
Bronchial cancer	2.7	6.1
Ovarian	6.3	6.3
Pancreas	3.6	3.6
Breast	none	8.3
Other (N=262)	none	---
TOTAL	4.7%	(carcin.)5.1%

Not all cancer types have the same propensity to metastasize in the ophthalmic region, even when the frequency of hematogenous metastases is high. Gastrointestinal malignancies only account for 2 to 3% of the ocular metastases in most reported series. Breast cancer, however, accounts for 30 to 70% of the diagnosed ophthalmic metastases. The long natural history of breast cancer and the tendency for multiple (up to 20%) and bilateral, (up to 40%), give further credence to the 'seed and soil' theory of Paget for metastatic growth.

Most reports discuss one aspect or one location of ophthalmic metastases, so that the relative incidence in the different parts of the eye and/or orbit is difficult to evaluate.
In the literature, the ratio of choroid to orbital metastases varies from 8/1 to 1/1. In most of the reported series, however, at least 50% of the metastases were located in the uvea, where the choroid accounts for a large majority. The report of Hutchinson et al. stated that 65% of the ophthalmic metastases, from different tumors are situated in the choroid, 24% in the orbit, and 10% 'elsewhere'.

Contradicting this, however, we cite Ratanatharatorn, where of breast cancer patients with ophthalmological meta-stases, 56% had choroidal and 34% orbital metastases. Bullock had more orbital metastases than choroidal in a series of 30 patients with breast cancer, but they apparently they included other ophthalmologic problems in their review.
When examination is done prospectively, about 60% of the patients will be asymptomatic and unaware of any ophthalmological problem. Albert et al. performed a prospective study in patients with breast cancer. They found choroidal metastases in 20% of the patients, with half of them asymptomatic.
The data of Mewis et al. are articularly interesting. In

152 symptomatic patients, they found 58 with choroidal metastases (38%) and in 98, asymptomatic stage IV breast cancer patients. 9 or 10% had choroidal involvement. Of all these patients, 40% had bilateral metastases.

It would also be interesting to know how many patients, currently accrued in actually ongoing trials for primary treatment, will later present with ophthalmic metastases. Kamby has reviewed the patients of the DBCG-trial (Danish Breast cancer Cooperative Group). In 863 patients followed for at least 7 years, they found 6 patients with eye problems, of whom 3 in the choroid. Together it accounts for only 0.7% of all patients. It should be remembered that 'trial'-patients are always 'low stage' patients.

The reported incidence is probably lower than in reality. Patients with any carcinoma are not routinely examined for ocular involvement. Ocular disturbances may be neglected because the patients' serious condition, while many patients also have age-related ophthalmic problems such as cataract. These patients are somewhat acquainted with any vision disturbances and many are seen outside specialized facilities and will not be accounted. Finally, subclinical metastases are frequently overlooked.

It may well be that since many patients are now treated by adjuvant hormonal or chemotherapy, the incidence is lower than before, but this is almost impossible to prove.

There are only a few series of autopsies where the eye status was examine (Bloch et al.). Gartner examined 230 patients with proven carcinomas from various sites and found 28 cases (12%). Of the 52 breast cancer patients, 37% had eye metastases. In a larger series, Nelson reported an incidence of 9.3% at cancer autopsies, including patients with leukemia and lymphoma, where the propensity for the eye to be involoved is well known.

Hagemeister et al. reported a figure of less than 1% eye metastases in autopsied breast cancer patients, but stated that the eye was examined only in a small number of them.

In an ordinary ophthalmology practice, metastases in the ophthalmic region are the most frequent tumor pathology after ocular melanoma.

According to Jeddi et al. there seems to be an increase in the incidence of ophthalmic metastases, from 7% up to 38%. There could bea number of reasons for this. Apart from developing better treatments for the proimary, use should also be made of more precise diagnostic techniques, as regular fundus examinations, ultra-sonography B, better photography and angiographic studies of the fundus. More patients are now being treated in dedicated centers.

As far as the metastases within the Uvea are concerned, 88% of the 950 consecutive patients in the series by Shields et al. were at the choroid, 9% at the iris and 2% within the ciliary body.

Pathways

Metastatic cancer cells will reach the orbit or the eye by the way of the arteria ophthalmica and its branches. According to Coman, the distribution of metastatic deposits may be related to the distribution of arterial emboli. Once a tumor cell reaches the bloodstream, its fate depends not on variation in susceptibility of different organs to growth of secondary tumors, but on the availability of tumor cells as an embol so that the frequency of metastases to various organs correlate with the number of cells reaching their capillary bed.

The much higher incidence of metastases in the posterior pole of the eye up to about 9:1 has attracted much speculation about the origin of this disproportion.

Duke-Elder, cited by Orenstein, has stated that emboli are more likely to arrive at the posterior pole of the eye through the approximately 20 short posterior ciliary arteries than through the 2 long posterior ciliary arteries or the 5 or more anterior ciliary arteries. However, there is no convincing evidence of a marked differential blood flow as resulting of this vessel distribution.

The extreme rarity af retinal metastasesas will be discussed further. This is at sharp variance with the behavior of infectious emboli, which characteristically implant themselves in the retina in more than 90% of cases.

Weiss has theorized about this. Compared with other extra-ocular target sites, the incidence of intra-ocular metastases is lower in breast cancer patients. However when the incidence of intra-ocular metastases is seen in relation to the calculated number of cells delivered via the arterial route, the uveal tract is the most favoured target site for the development of metastases per unit of delivered cancer cells. It would seem that aside from hemato-rheological aspects, it must be that the soild of the choroid is very propitious for the growth of metastatic cancer cell (seed), according to Paget's hypothesis.

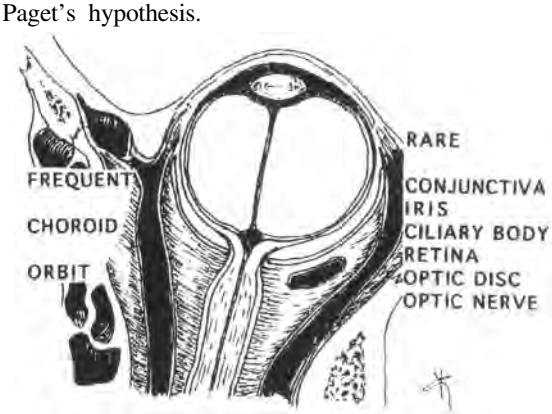

Fig. 6.4 - Frequent and rare metastatic location of ophthalmic metastases.

In a few cases there may be indirect invasion of the orbit from bone metastases in the orbital wall, with compression of the different ocular muscles.

The interval between first sign and diagnosis is remarkably short, probably because patients will consult at an early stage, although it can extend up to 6 months. The process will then be rather extended and dramatic.

Ocular metastases can be found in the epibulbar region, the iris, the ciliary body, the choroidea and in the retina.
It is well-known that the majority, (about 80%), of all metastases in the eye region are within the globe. Except for one author a predilection for a particular side has not been noted. Uveal metastases are the most frequent intra-orbital location of metastatic disease. They account for more than the two-thirds of the ophthalmological metastases and for more than 80% of the intraocular localisation. Of those in the uvea, up to 90% are in the choroid. Locations in the ciliary body and the iris are much rarer.

In about half the cases only the posterior segment is involved, 40% the anterior segment and 10% only the anterior segment. Many are multiple and bilateral even metachronous.
The sector of the choroid most frequently involved seems to be the temporal: 75% of the 40 surveyed patients (Thatcher et al.).

Symptoms

The main problems are firstly accurate diagnosis of the likely metastatic cause and secondly precise localisation of the metastases causing the symptom(s).
When the patient is known to have been treated previously for a cancer, any ocular complaints should be carefully checked for a possible metastatic origin. Such symptoms can be caused by a large number of ophthalmologic pathologies, so that an extensive differential diagnosis has to be considered.
The symptomatology of any ophthalmic metastasis depends largely on the subsite of the involved eye.
Patients with metastases in the eye or orbit present with many different and aspecific complaints:

Eye Displacement,
Ptosis or Enophthalmos,
Vision Problems: blurring, partial, diplopia
Pain within the eye or orbit.

Displacement of the eyeball is a frequent symptom, resulting most frequently in exophthalmos or proptosis and seldom in enophthalmia. This will be discussed later.
Vision problems are usually partial, sectorial and rarely involve total vision loss. Snow storm impression or blurring sight is not unusual. It can also include, apart from these field deficits, scotomas, phosphena, metamorphopsias (distortion of object shape) and myodesopsias (vision impaired by difficult muscle motion) may be involved. Photophobia and xanthopsias (seeing yellow light), loss of colour vision and floaters have also been reported.These symptoms can be caused by metastases in the anterior segment but much more frequently by those in the posterior segment of the choroidea. Another rare location of metastases causing vision problems is the corpus vitreum.
Diplopia is almost always caused by a paresis of the VIth nerve. Its involvement can be meningeal, at the skull base or in the orbit. Radiology and scintigraphy, but especially CT or MRI are very sensitive methods enabling accurate location of the lesion.

Palsies can be caused by metastatic conditions affecting the cranial nerve from within its origin in the mesencephalon, along its course beneath the brain in the subarachnoidal space, the penetration depth to the skull base down to within the orbit. It would seem that the last segment from skull to orbit is the most frequently involved.
A few authors have discussed this question. Richards et al. have examined the various reasons for the paralysis of the oculomotor, the trochlear and the abducens nerve in more than 4000 cases. A neoplasm was the cause of the palsy in 757 (18%) of these patients. Of all the patients with an oculomotor palsy, a tumor was responsible in 12.4%, for a paralysois of the trochlear 4.8% and for the abducens nerve 21.5%, confirming the well-known clinical impression everyone has of the high frequency of abducens paralyses in an oncological setting. The same authors found in their own series of 1278 ocular palsies, that 193 (15%) were caused by a tumorous condition, the majority being from metastases (36 patients) or meningioma. The other tumors were primaries of the nasopharynx, pituitary tumors, chordomas and many others. To give precise figures for the number of metastatic conditions, the abducens was concerned 30 times, the oculomotor 6 and the trochlear 4. Four patients had two or more palsies. The primaries were however not reported. Berlit reported that 11% of the abducens palsies had a tumoral origin. Brazil had similar data on trochlear nerve palsy.

Table 6. 5- Oncologic Causes of Ophthalmoplegia
Modified from Kattah et al.

1. Leptomeningeal Carcinomatosis
2. Increased intracranial pressure
3. Metastases at the skull base:
   - Metastases in the Orbit
   - Parasellar metastases
   - Metastases at the apex petrosus
   - Metastases at the clivus
   - Brain stem metastases
4. Metastases in the Oculomotor Muscles
5. Opportunistic meningeal infections
6. Side effects of chemotherapy
7. Radiation induced cranial neuropathy

If the palsy is of meningeal origin, many other neurological symptoms will accompany the clinical situation.
A particular form of palsy is the metastatic involvement of the eye muscles, which can be part of or the sole problem in an orbital involvement (table 6.5).

Another problematic situation is a patient presenting with uni- or bilateral vision defects up to the bitemporal hemianopsia. This can be complicated by pain, also with some ophthalmoplegia and diabetes insipidus, or more rarely by anterior hypopituitarism.

The Claude Bernard Horner syndrome consists of a group of symptoms: unilateral miosis, enophthalmia and narrowing of the palpebral fissure.
This syndrome occurs when the upper sympathetic chain is involved somewhere between its cranial origin at the base of the skull and its postganglionic end within the eye and orbit, along its course in the neck, the upper thorax and back to the neck.
There are many possible anatomical points where this nervous chain can be disrupted by a tumorous condition.When a patient presents with this syndrome a clinical and imaging study should be performed from the skull base down to the upper thorax.

This nerve chain consists of three neurones; the first (brainstem-cervical cord) from the hypothalamus to the lateral grey matter in the thoracic spinal cord (Th1 level), the second from Th1 to a synapse within the superior cervical ganglion; the third (postganglionic) are parasympathetic fibers running along the internal carotid artery through the ciliary ganglion and ending in the iris.
Instillation of 4% cocaine solution in both eyes dilates a normal and a small pupil, but not a sympathetically denervated one. This confirms the diagnosis but cannot locate the cause. Hydroxyamphetamine 1% releases norepinephrine from synaptic vesicles and will dilate the normal and the small pupil if the lesion is postganglionic. If no dilation occurs, the lesion is postganglionic in the third neurone.

Metastases within the orbit, particularly at the ciliar ganglion, also can provoke the syndrome.

Pain can also be reported by the patient. The pain can be localised around the orbit due to invasion in the orbital walls. It can be felt within the orbit, together with some hindrance or painful globe movement due to invasion of the orbital content or/and the muscles. But pain can also be caused by the involvement of the globe resulting in increased intra-ocular pressure even with some glaucoma, or a reactive reaction as iridocyclitis (Woog et al.). Metastases in the sclera are very rare (Yeo et al.).

Any of the signs mentioned above can be caused by any metastases at specific or various locations within the eye, the orbit or the optic tract up to the posterior lobe of the brain.

Ophthalmic problems or symptoms can also result from metastases in the cranial base, including the orbital walls, in the meninges and within the visual pathways up to the sulcus calcarinus in the occipital lobe. While metastases in the occipital lobe are less frequent than in other lobes, the incidence of this location as a cause of vision loss is rare.
Metastases within the orbit, even in the ocular muscles can be uni- or bilateral. Bilateral orbital metastases have been reported.
We would finally mention the symptoms of metastases at the eyelid with a degree of inflammation. This is discussed laterr.

It should, however, be remembered that many patients are completely asymptomatic. In the series by Mewis et al., about 9% of the patients with mammary carcinoma and choroidal metastases had no complaints. We have previously cited the prospective study by Albert et al.

Fig.6.5 presents the diagnotic flow-chart for ophthalmic metastases.

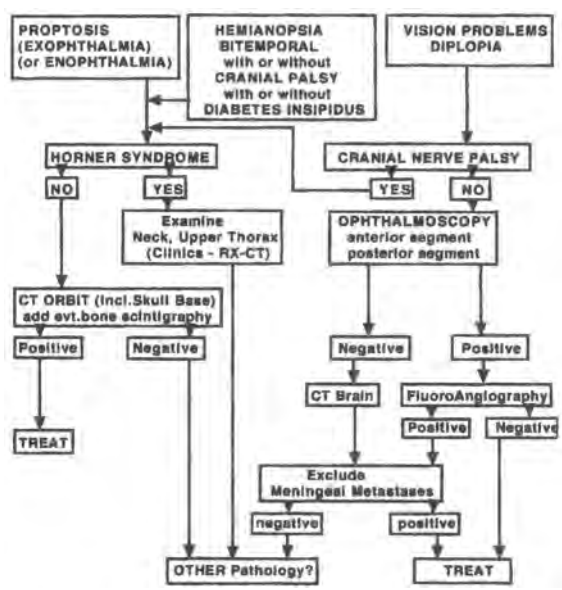

Fig.6.5 - Algoritm for the diagnosis of oncologic ophthalmopathies

METASTASES to the ORBIT

Pathways

As lymphatics are absent from the orbit, metastases in the orbit occur through hematogenous spread. These metastases must be distinguished from the contiguous invasion that can occur from various other sites: facial tumors, either soft tissue either bony, invading the orbit, but also sinonasal carcinomas. On rare occasions, nasopharyngeal or also brain tumors can in-

vade the orbit.

Incidence

According to Henderson, 7% of 465 orbital tumours examined, were of metastatic nature. The relative frequency of metastases in the orbit accounts for about 10 to 25% of all ophthalmic metastases.
Orbital metastases account for 1 to 3% of all orbital disease (Volpe et al.). Haye et al. found the left orbit to be more involved than the right. They explained this as being related to the more direct arrival of the left carotid artery.
Shields and Shields reported that 26% of the patients presenting with orbital metastases had no known prior history of cancer. In about half of them (12%) no primary could be found. In 18 of the 21 women, breast cancer was the primary involved. 14 of them were aged between 60 and 79 years.

Primary Tumors

Of the 645 lesions in the orbit surveyed by Shields et al., 16 or 2.5% were metastatic tumors and 70 (11.0%) from invasion by adjacent tumors. Of the sixteen metastatic tumors, 12 were from a breast cancer, 2 from a prostate and one bronchus and colon cancer. The largest survey on this subject was made by Goldberg et al. in 1993 and covers 207 cases. Nearly half of them originate from breast cancer (table 6.6).

Table 6.6 - Metastases to the Orbit
Primaries involved (N=207 patients)
Literature Data Reviewed by Goldberg et al.1993

Primary		by Gender M(°)	F(°)
Breast cancer	42%	--	56.7%
Bronchus	11%	4.8%	<1
Unknown	11	3.2	<1
Prostate	8.3	35.7	--
Melanoma	5.2	13.8	5.9
Gastrointestinal tract	4.4	4.8	4.2
Kidney	3.2	9.7	3.3
Other (‘)	13%	22.7	12.7

(‘) see text
(°) 123 men and 118 women.

Except for those mentioned in table 6.6, the other primaries concerned were neuroblastoma, testis, adrenal, pancreas, thyroid, bile duct, carcinoid, sarcomas, ovary, parotid, uterus.
The relative distribution is probably not correct as is the case with all clinical and autopsy series. Examination of the eyes is not systematically done in all metastasized cancers not even at autopsy. Nevertheless it is clear that breast cancer is the most frequent primary involved for the whole group and for women, but although never stated, prostate cancer is the main cause in men (35.7%).

Silva reports that of 300 patients consulting for exophthalmos 7 or 2.3% were from a metastatic tumor. In a series of 28 orbital metastases (Font et al. Ferry), breast cancer accounted for 62% (8/13) of the female patients.
In the Danish National Register, Johanssen et al. retrieved 965 cases of orbital space-occupying lesions, over a period of 23 years. While 23% concerned local ex-tension of ocular or neighbouring tumors, only 36 or 3.7% involved true distant cancer.

Type 1 Metastases

A large number of the patients presenting with orbital metastases had a known oncology history. Sometimes however patients do not or do not want to mention this, or even have forgotten it. Indeed, there may be a time lapse of decades.
The already cited review by Goldberg et al. found that in 42% of the patients the orbital metastases preceded the diagnosis. This means that the ophthalmologist consulted has a heavy responsibility in such cases.
They found from the literature review that occult cancers are more common in bronchial or renal cancers, both well-known for this particulartity. (see the relevant Chapters). More data areshown in fig. 6.6.

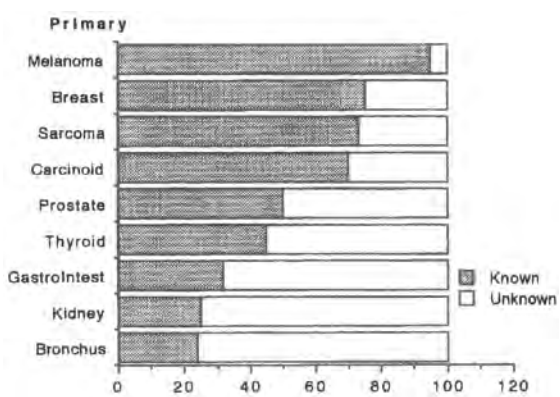

Fig.6.6- Proportion of occult tumors at presentation with orbital metastases for different primaries (redrawn from Goldberg et al.)

Symptoms

As already mentioned, further proptosis of the eye or exoph-thalmos is the main symptom of an orbital involve-ment.
Enophthalmos is relatively rare but has to be differentiated from Horner’s syndrome. De Keyzer et al. collected 16 cases, including two from their files, of which 12 had a breast cancer.
Initially, the relative abruptness and disproportionate number of symptoms is an indication of metastatic disease, compared to another space-occupying orbital lesion (Volpé et al.).
The hallmark of a metastasis in the orbit is exophthalmos (proptosis), which is present in 75% (Font et al.) of the cases with orbital involvement. Less fre-

quent are pain (29%), vision impairment or loss (29%) and periocular or orbital edema (25%). Font et al. found that in up to 50% of their cases, orbital metastases were the first manifestation of a primary tumour, including mammary carcinoma. Palpable masses are also frequently reported.

The direction of displacement of the eyeball resulting in proptosis or exophthalmos is determined by the location of the metastases within the orbit. Expansive metastases of its bony wall, usually retrobulbar will lead to a lateral propulsion of the eyeball. Metastases at the top of the orbit (intraconal) will result in a forward propulsion.

In about 20% a tumor can be seen in the eye region.

Ophthalmoplegic symptoms due to invasion either of the muscles or of the nerves, and usually resulting in strabismus or diplopia occur in only 18% (the 3rd, 4th or 6th nerve), with another 7% presenting with ptosis of the upper eyelid. This can be explained within a Horner's syndrome.

In general terms, orbital metastases can present as four different basic syndromes (Ainbinder et al., table 6.7).

Table 6.7 - Metastases to the Orbit
Clinical Presentations
Modified from Ainbinder et al.

Mass	Primary mass effect, palpable or displacing the globe
Infiltrative	Diffuse or localized, with diplopia, enophthalmos, frozen globe and a firm orbit. Frequent in scirrhous breast cancer
Inflammatory	Acute or subacute onset. Brawny induration, unrelenting course. DD. with cellulitis, myositis, orbital pseudotumor
Functional	Cranial nerve palsy out of proportion to mass or infiltrate

Pathology

The sites of metastasis within the orbit, according to the small series, are the same in the different quadrants. The literature review by Goldberg et al. concluded that there was a higher incidence within the lateral (39%) quadrant. 32% of the metastases were found in the superior quadrant, 12% in the inferior and 20% in the medial. The majority of orbital metastases are not encapsulated, poorly marginated and diffusely infiltrating the orbital structures. The metastases can involve the bony orbit, specifically the extraconal space, the lacrimal gland, the intraconal fat, the extraocular muscles and other ocular structures (Peysler et al.).

Metastases in the ocular muscles were also reported. They will result in uncommon types of paralyses of the eyeball, sometimes complicated by exophthalmos.

Although most authors state that there is no Le/Ri difference in the incidence, the literature survey by Goldberg et al. disclosed a significant Right preference (p=0.5) (table 6.8). This is the case for most primaries.

Table 6. 8 - Metastases to the Orbit
Site preference according to Primary
Literature Review by Goldberg et al.

Tumor	Left	Right	Bilateral
Breast cancer	20	26	10
Prostate	17	25	1
Melanoma	13	11	0
Kidney	5	11	1
ALL patients	95	116	17

The orbital metastases can present in the different clinical forms, delineated by Goldberg et al.

1. Primary mass causing axial or non-axial displacement of the globe. The mass can be palpable.
2. A diffuse or localized infiltration characterized by diplopia, enophthalmos, limitation of eye movements or frozen globe and firm orbit at palpation.
3. Decrease in cranial nerve function out of proportion to mass or infiltration.
4. Acute or subacute onset of inflammation and other symptoms such as chemosis, injection, pain on eye movement, erythema and lid swelling.
5. Asymptomatic, only found at clinical or imaging studies.

Their literature review produced the data as in table 6.9.

Table 6.9 - Metastases to the Orbit
Signs and Symptoms (N=207 patients)
Literature Review by Goldberg et al.

Complaints		Observed Signs	
Diplopia	38%	Proptosis	64%
Proptosis	35	Motility disturb.	58
Pain	23	Palpable mass	27
Decreased vision	20	Blepharoptosis	21
Blepharoptosis	16	Decreased vision	22
Mass	13	Displacement	18
		Chemosis	15
		Enophtalmos	10
		Disk edema	8
		Retinal fold/striae	4
		Paresthesia	3
		Pulsation	1.5%

Enophthalmos is reported in 7%-10% of the cases and has been extensively discussed by De Keyzer et al.. The presenting symptoms are diplopia, drooping of the upper eyelid or narrowing of the palpebral fissure, and occasionaly orbital pain. Enophthalmia results from the invasion of the orbit, whereby the muscles, nerves and surrounding soft tissue become so entwined and infiltrated with the tumor that the eye becomes immobilized and pulled backwards. Enophthalmos as metastatic phenomenon is caused by a mammary carcinoma in 60%.

At the time of diagnosis, an uncapsulated tumor

growth with diffuse involvement of the various orbital structures will often been found, although initially tumor emboli may lodge in muscle, fat or bone. Adjacent bone destruction occurs in approximately 60% of the cases. Sixty percent of the lesions are extraconal, 20 % intraconal and 20% both. Moreover evidence of intracranial disease either by direct extension or as discrete metastases is present in 65%. The most common feature at CT is a mass lesion followed by some bone involvement.

To what extend this is part of a Claude-Bernard Horner syndrome is not clear, since the pure Horner syndrome contains all of these symptoms, except diplopia. Casanovas asked the same question in his literature review on metastatic lesions in the eye and orbit.
Cline et al. reviewed 26 cases of enophthalmos and found three common causes to be orbital asymetry, trauma and orbital metastatic disease. The last included four cases of which three were breast carcinoma.

Diagnosis

The mainstay of diagnosis are computer tomography studies which can or should be supplemented by fine needle aspiration biopsy.
CT findings for 22 metastatic orbital tumors were reviewed by Healey. Some patients with invaded orbits were included. The large majority (18/22 or 82%) had a detectable proptosis. Extraconal metastasis was seen in 59%, while only a few had intraconal invasion only. In 46% there was evidence of intracranial extension, either to the frontal or temporal lobe. Adjacent bone destruction was visible in 68%. Similar data were reported by Goldberg et al. (table 6.10).

Table 6. 10 - Metastases to the Orbit
CT findings in 28 patients
Data of Goldberg et al. 1990

Tumor tissue localization		Quadrant localization	
Bone	40%	Medial	40%
Intraconal mass	44	Lateral	25
Muscle	16	Superior	20
Diffuse	12	Inferior	15

METASTASES to the OCULAR MUSCLES

Metastases within the ocular muscles deserves a special interest, as its symptomatology is specific.
Of 137 cases of enlargement of the extra-ocular muscles noted on CT, 7% were due to metastatic disease (Rothfus). At CT, the involved muscle has usually a segmental area of widening, often with an irregular border against adjacent fat, and may have associated bone destruction. Diffuse muscle involvement can also be seen (Peyster et al.).
Discrete involvement of these muscles is an event rarer than the incidence of orbital metastases. Up to 1990 there had been only case-reports, reviewed by Capone et al., when they reported on 5 cases (table 6.11).

Table 6.11 - Metastases to the Ocular Muscles
Literature Review by Capone et al. 1990

Primary		Muscle concerned	
Breast Cancer	16cases	Rectus superior	25
Melanoma	6	Rectus (vertical)	9
Kidney	2	Rectus Obliq.	1
Unknown	2		

and one case of
Carcinoid, stomach, Merkel carcinoma

About half of the cases were from a breast cancer, while melanoma was the second most important. One strange aspect is the high number of cases with involvement of the rectus superior. This could be ascribed to the fact that this muscle is best visualized with CT on axial CT and because the muscle is the largest.
According to Rothfuss et al, neoplastic disease results in enlargement of the muscles in two ways. The first one is by compression of venous outflow from the muscles at the orbital apex. The other way is by direct invasion of the muscle, associated with destruction of the orbital wall, contiguous soft-tissue masses or dilatation of the ipsilateral cavernous sinus.

A few other cases have been reported since this review, among them one from a thyroid cancer.
Symptomatology is mainly diplopia due to impaired function, possibly with proptosis and pain. CT is the best diagnostic imaging method, if needs supplemented by biopsy.
Of the five cases reported by Capone et al., two were first presentation.
Differential diagnosis with several other ophthalmologic pathologies is mandatory.

METASTASES to the IRIS

Metastases to the iris are usually detected when they are still relatively small. The first case of this rare metastases was described by Smoleroff et al. al. in 1934. Four years later, Sanders wrote on a few cases of metastases to the iris. We were unable to trace the first report.

Primaries

The largest series was reported by Shields et al. with 43 eyes. The most frequent primary was breast cancer (table 6.12).

Bibliometry

In our files we have 40 reports on metastases in the

iris: 4 concerned breast cancer, 4 bronchial cancer, 2 carcinoids, 3 uterine cancers, 2 melanoma, 1 neuroblastoma, 4 kidney, 1 pancreas and 2 thyroid. Seventeen additional reports concern small series.

Table 6. 12- Metastases to the Iris
Primary Involved (N=43 eyes)
Series of Shields et al. 1997

Breast cancer	17 eyes
Bronchus	8
Skin Melanoma	4
Gastrointestinal tract	2
Kidney	1
Adrenal	1
Prostate	1
Bone tumor	1
Unknown primary	8

Symptoms

For metastases within the anterior segment the most frequent first symptoms are diminution of vision or even a visible tumor each in 60% of the cases.
Redness of the eye can be an initial manifestation. Iridocyclitis is present in 40% of the metastases to the anterior segment. As reported by Ferry et al. in some cases, the diagnosis of metastasis was only made after enucleation. Glaucoma occurs because of obstruction by sheets of tumors, infiltration of the trabecular meshworks and emissary vessels by neoplastic cells. When the tumor lobules break through the confines of the uvea into the anterior chamber angle or through a peripheral anterior synechia, a closed-angle type glaucoma occurs.
Hyphema is only rarely reported. Other authors, Raymond for example mention some deformation of the iris.

Metastasis in the ciliary body (Shields) can be contiguous to an iridial or choroidal invasion. They can attain larger sizes than choroidal or iris metastases because of their more cryptic location. They have a propensity to produce a clinical picture of chronic iridocyclitis that is generally unresponsive to steroids. Some ciliary body metastases have a large sentinel vessel on the overlying sclera, similar to that seen with some ciliary body melanomas.

Pathology

There may be one or more yellow or white lesions, except when melanoma is the primary, when they are brown or black. The metastases of a renal cell carcinoma and carcinoid are orange.
The majority of the metastases were located in the inferior quadrant (42%) (table 6.13).

These metastases seem to be somewhat friable and can shed tumor cells into the aqueous, producing a deposit of cells in the inferior portion of the anterior chambers resembling hypopyon. Differential diagnosis with endophthalmitis can be difficult when the metastasis is accompanied by an inflammatory reaction. A further examination of the eye is necessary to exclude other metastatic lesions. Fine needle aspiration biopsy is a convenient and rather safe method for establishing diagnosis.

Table 6.13 - Metastases to the Iris
Quadrant involved (N=43 eyes)
Series of Shields et al. 1997

Superior Quadrant	7 or 16%
Nasal Quadrant	9 or 21%
InferiorQuadrant	18 or 42%
Lateral Quadrant	6 or 14%
All quadrants (diffuse)	3 or 7%

Metastases in the uvea are by far the most frequent ocular metastases. They are almost all situated in the posterior choroidea.
The deposit is usually visualized at ophthalmoscopy as a flat yellowish-grey area and such areas may be multiple. Retinal detachment (solid or fluid) are commonly associated findings, in up to 20% of the patients.
They are also described as one or more homogenous creamy yellow choroidal lesions. With the exception of metastatic melanoma, a choroidal metastasis lacks intrinsic pigmentation, although overlying alterations in the retinal pigment epithelium are common. Most larger symptomatic lesions produce a secondary retinal detachment in up to 20% of the patients.
The configuration of the metastases can range from placoid to dome-shaped, but it almost never assumes a mushroom shape. If an amelanotic tumor is mushroom shaped, it is much more likely to be a melanoma rather than a metastatic tumor.

Choroidal metastases often produce chronic degeneration of the overlying retinal pigment epithelium, most often characterized by patchy golden-brown deposits on the tumor surface. These deposits become pronounced after treatment with radio or chem-therapy. They have been shown to be composed primarily of macrophages containing lipofuchsin pigment liberated from damaged retinal pigment epithelium cells.

CHOROIDAL METASTASES

Choroidal metastases are, in fac, the smallest metastases that can be detected in vivo. Fluoroangiography should detect metastases of 1 to 2 mm^3.

Primaries

There is very large body of literature and case reports on choroidal metastases. The series by Shields et al. contains 479 eyes or 53%. The primaries are listed on table 6.14. The large majority are breast cancer patients.

Data according to gender are not at hand, but the most frequent are probably breast in women and bronchial cancer in men.

Table 6. 14- Choroidal Metastases
Primaries involved (N=479)
Series of Shields et al.

Breast cancer	252 eyes or 53%
Bronchus cancer	98
Gastrointestinal tract	18
Prostate	10
Kidney	8
Skin melanoma	5
UNKNOWN	71 eyes or 14.8%
Thyroid, bone, adrenal, pancreas, bileduct, ovary, testis each 1	

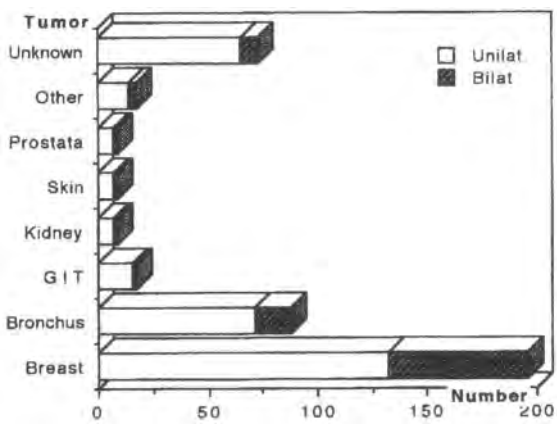

Fig.6.7 - Primary Site in patients with uni- or bilateral metastases within the uvea (drawn from data of Shields et al.)

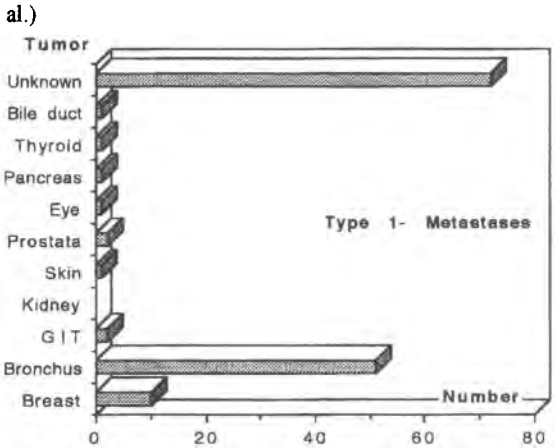

Fig.6.8 - Primary cancer site in patients presenting with uveal metastases as first manifestation of their cancer (N=142) (type 1 metastases). Redrawn from data of Shields et al.

Bilateral involvement is not rare and most frequent in breast cancer patients (fig.6.7). Quite a large number of patients present with choroidal metastases of an up to that point unknown primary (fig.6.8).

Choroidal metastasis can be the first symptom of an unknown mammary tumour. It can, however, also occur many years, (even more than 20) after the diagnosis of the primary.

More than 90% of the metastases in the anterior segment are from a mammary cancer (in women) and in 75% from bronchogenic carcinoma in men.

Recently, Shields et al. reported on 40 cases of iridial metastases. Of the 25 women with iris metastases, 16 or 64% had breast cancer. In one of them the breast cancer was detected after diagnosis of the iridial metastases. They were unable to discern a preferential site for these metastases, although a slight prevalence in the inferior half appeared.

Pathology

In 6.5% of the breast cancer patients the diagnosis of uveal metastases preceded the diagnosis of mammary cancer. More than 45% of the metastases occurred more than 5 years after the primary breast cancer diagnosis.

Of their 98 patients with uveal metastases, Zografos et al. found 26 cases (26%) with bilateral lesions. 42 patients had multiple lesions, of which 20 were unilateral metastases.

More details were provided by Shields et al. from a series of 479 eyes (table 6.15).

Table 6. 15 - Choroidal Metastases
Pathologic Features (N=479)
Series of Shields et al.

Radial location	Superior	103 (22%) (')
	Nasal	67 (14%)
	Inferior	83 (17%)
	Lateral	167 (35%)
	Macula	59 (12%)
Mean diameter base 9 mm, median 8 mm (')		
Mean thickness 3 mm (median 2 mm)		
Surface configuration	Dome-shaped	152 (32%)
	Mushroom	2
	Plateau	325 (68%)
Color Yellow	448 cases (94%)	
Brown-gray	17 (4%)	
Orange	14 (3%)	
(') considering only the largest metastasis		

Symptomatology

The most frequent first symptom is partial or complete loss of vision (80%), pain in about 14% and photophobia or scotomas in another 13%. The symptoms are bilateral in about 20% of the patients.

Detailed information on symptomatology was provided by Stephens et al. in respect of 70 patients (table 6.16), correlated with the duration of symptoms before diagnosis.

Beati et al. have discussed this more extensively. Among 133 patients, of whom 73 with breast cancer, they noted 97 cases (75%) with scotoma in 16%,

phosfenes in 11%, metamorfopsias in 10%, ocular pain in 10%, but also myodésopsias, eye inflammation and some other not specified complaints, each in about 5%. In 6.5% of the diagnosed metastatic tumors no primary could be found.

Table 6. 16 - Choroidal Metastases
Symptomatology in 70 patients
Data of Stephens et al.

Symptom	Incidence	Duration before Diagn
Blurred Vision	80%	7wks (1-52)
Pain	14%	4 (1- 8)
Photopsia	13%	11 (2-52)
Red eye	7%	8 (2-20)
Floaters	7	9 (2-16)
Field defect	3	
Photophobia	1	
Iris lesion	1	
Asymptomatic	6	

A classification of the extent of involvement was proposed by Chu et al.: grade I being less than half of a quadrant, grade II more than half of the quadrant of the eye ground, with no retinal detachment, and grade III more than half of the quadrant with moderate to massive detachment of the retina. For Hennequin et al., grade I means less than a quarter, grade II more than one quarter and grade III includes retinal detachment. This classification was modified later by Panizzoni et al. who graded according to retina halves. A typical view of choroidal metastasis is on fig.6.9.

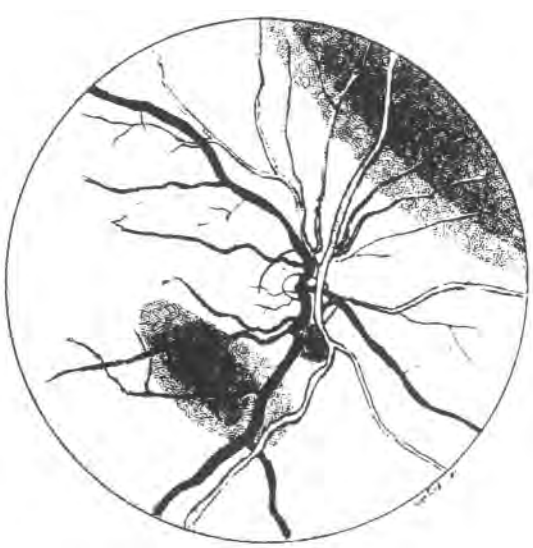

Fig.6.9 - Fundus view of a choroidal metastasis. The shaded areas correspond to elevated retina (from Cieplinski et al., with permission)

An important problem is differential diagnosis with intra-ocular melanoma. At ultrasonography there are several features allowing differentiation. A study compared 16 breast cancer metastases with 66 melanomas (Sobottka et al.) (table 6.17).

From these data, it would seem that the combined use of height to base ratio and reflectivity allows a highly significant discrimination between choroidal melanomas and metastases, at least from breast cancer.

Table 6.17 - Ultrasonography of the Choroid
Differentiation between Melanoma and Metastases
Data of Sobottka et al.

Feature	Metastases N=16	Melanoma N=66	
Dimension height	0.8-8.0mm	3.5-21.0mm	
mean	2.7	8.3mm	
base	4.3-16.3mm	4.4-22mm	
mean	12.4	12.8mm	
Ratio height/base	0.08-0.31	0.23-0.95	
mean	0.18	0.6	p<0.001
Reflectivity	60-90%	0-70%	p<0.001
Shape polygonal	13/16	6/66	
dome-shaped	3/16	46/66	
mushroom	none	14/66	p<0.001
Choroid Excavation	none	38/66	p<0.001

CILIARY BODY METASTASES

Shields reported a series of 21 eyes with ciliary body metastases. The tumor appeared as a yellow sessile or dome-shaped mass in the ciliary body region. They are difficult to visualize directly.
There is a slight preponderance of breast cancer as primary (table 6.18). It will be seen that one third are from an unknown primary.

Table 6.18 - Metastases to the Ciliary Body
Primaries involved (N= 21 eyes)
Series of Shields et al. 1997

Breast Cancer	4 eyes
Bronchus	2
Gastrointestinal	2
Kidney	1
Prostate	1
Adrenal	1
Unknown Primary	8

METASTASES to the RETINA

Metastases to the retina are very rare. A review of the literature by Leys et al. found 11 cases from a carcinoma and 11 cases from a melanoma, to which they added two other cases, one from a bronchial carcinoma and one from a breast cancer. The large majority of these metastases remains probably remains undetected in the clinical setting.
A review by Mack et al. mentions 20 cases (table 6.19). There were 14 men and 6 women. Three patients had bilateral involvement. In five patients the primary was unknown at presentation (type 1 metastases). The tumor cells probably reach the retina through the internal carotid artery. This explains why many also have brain metastases.

Table 6. 19 - Metastases to the Retina
Primary Tumors
Literature Review by Mack et al. (1997)

Skin Melanoma	8 cases
Bronchus carcinoma	6
Gastrointestinal	2
Genitourinary	1
Breast cancer	1
Unknown (adenocarcinoma)	1

Symptomatology

Decreased vision was the main complaint. In half of the patients, floaters were mentioned. Diplopia is rare. Twenty percent were symptom-free at examination.
The positive ophthalmoscopic and fluoresceine findings were limited to a single white retinal plaque with a discrete serous retinal detachment and a few hemorrhages on its borders.

Pathology

Unlike choroidal metastases, retinal metastases are less cohesive and may cause vitreous seeding, often after invasion of the superficial retina and retinal vessels (Shields et al.). In the case with breast cancer (Leys et al.), collections of cells were suspended in the posterior vitreous in front of the retina. Ophthalmoscopic examination and fluoresceine angiography revealed leaking retinal vessels in the affected area.
The vitrectomy specimen revealed metastatic cells only in the electron microscopy studies.
In the case discussed by Piro et al., the diagnosis was patholo-gically confirmed post-mortem, although there were known metastases in the vitreum. Zweifach reported the clinical observation of moving retinal and choroidal emboli in a patient with breast cancer. In these two cases and the one reported by Leys et al. no mass was visible in the retina, but was recognized by microscopic study of the retina in the surgical specimen. These are the only pathologically confirmed cases of metastatic retinal pathology from a breast cancer.
A retinal metastasis may be indistinguishable from an ischemic infarct of the retina. On the other hand they seem to be much more visible in cases of metastatic melanoma where pigmented metastatic lesions can be seen in the retina and choroid.

Bibliometry

We have found 23 reports specifically on retinal metastases: 5 bronchial cancer, 2 breast, 1 carcinoid, 6 melanoma, 1 myxoma of the heart, and 1 esophageal cancer. Eight reports were not located.

METASTASES to the VITREOUS

Vitreous metastases are very rare. These patients, mainly with metastatic skin melanoma, present with symptomatic floaters.
We found 7 reports in the literature of which 4 concerned melanoma, 2 breast cancer and 1 bronchial cancer.
According to Pollock et al., there may be many indications that the site of origin is the optic nerve. At histology, the vitreous metastases form discrete non-inflammatory spherules, with a linear array emanating from the vicinity of the disc. The most superficial of these projections have attenuated attachments and appear to be in the process of separating. Most patients have either retinal or ciliary body metastases (Watkins et al.).

METASTASES to the EYELID

Although the eyelids have a rich vascular supply, there is no evidence to implicate them as a particularly fertile field for tumor cell implantation. Arnold raises the possibility that implantation could be facilitated at sites of acute or chronic chalazion inflammation due to the increased blood flow and vascular permeability at during such a period. The majority of eyelid metastases however, occur without evidence of prior or concurrent chalazion. In all probability, the metastatic tumor mass obstructs Meibomian glands and facilitates chalazion formation as a secondary event.

Metastatic tumors of the eyelid are rare, their frequency being reported as less than 1% of the malignant tumors of the eyelid. The primary focus is most frequently breast cancer, accounting for between 35 and 65%. They may be bilateral.
The first case of eyelid metastases from a mammary carcinoma was reported by Grönvall in 1953. A literature review by Arnold in 1985 revealed that 26, or 65% of the 38 cases of metastatic eyelid cases were from a breast cancer.
A literature survey by Mansour et al. in 1988 found 88 reported cases, to which they added 49 new cases from their own files. In both groups breast cancer accounted for 47%, whom both genders were taken together. But in their own cases 63% of the female patients had breast cancer.
In 1995,Zhang et al. made a new review and found that for the breast cancer cases the right eye was much more involved, 22 against 8 and in another 2 in both sides. The upper eyelid was involved in 13, the lower in one and both in eight. On the contrary, Riley reported twice more in the left lid, for all primaries. In his series there were 8 breast cancer patients with an equal number of metastases to each side.
In respect of the age-related incidence of eyelid-metastases in breast cancer, their peak incidence lies in the age group of 50-59 years (75% of the patients).
Of all malignant eyelid lesions, they form less than 1.5%.
As far as the primaries are concerned, a review was published by Arnold et al. which described 49 cases and a series of 49 cases was reported by Mansour et al.

They are grouped together in table 6.20. It will be seen that breast cancer accounts for more than half of the cases.

Table 6.20 - Metastases to the Eyelid
Primaries involved (N=90)
Literature Data (Arnold et al. and Mansour)

Breast cancer	50 cases		
Melanoma	8	Other(')	5
Bronchus	7	Carcinoid, Trachea	
Kidney	6	Colon, each one	
Stomach	4		
Parotid	2		
GastroIntest.tract	2		
Unknown	3		

(') no further details

Pathology

Painless isolated indurations or diffuse swellings, sometimes accompanied by reddening of the skin, is the usual presentation. Ulceration is rare. Differential diagnosis with hordeolum or chalazion can be difficult.

Mansour et al. reported on a long list of diagnoses first proposed before the lid metastases recognized as such: cyst, xanthoma, sty, granuloma, xanthelasma, mucocele, fibroma and some others.

Eyelid metastasis often occurs in the advanced stages of the disease. According to the literature about 70% of these patients already have other metastases. Only in one case mentioned by Costner was it the first symptom of a breast cancer.

Riley has classified eyelid metastases into three types according to clinical features:

Type 1 (62%) shows solitary subcutaneous nodules, non-tender and without inflammation. The nodule can be palpated as a painless induration This is the most common type and is mostly observed in malignant melanoma. Differential diagnosis with chalazion complicated by inflammation can be difficult.

Type 2 is a non-tender thickening and induration in the eyelid (30%) usually observed in mammary carcinoma. Painless edema with induration in the whole lid is described, but no signs of inflammation. It has been mistaken with myxedema atopic dermatitis and cellulitis.

Type 3 (8%) involves an ulceration of the eyelid.

Arnold introduced a fourth type (5%), an acutely inflamed tender nodule.

It seems probable that some of these reported cases, in view of the edema mentioned of both lids, in fact had also orbital infiltration, extending into the eyelids.

Cytological examination after fine-needle biopsy is the mainstay of diagnosis, this being a simple method. Whatever method used, CT examination to explore any further extension is mandatory.

METASTASES to the CONJUNCTIVA

This site has hardly received any attention in the literature. Except for a small number of case reports, Kiratli reported a series of 10 cases. This confirms the rarity, in spite of the fact that the conjunctivae are a frequent site of pathology in common ophthalmologic practice.

A review of 2,455 conjunctival lesions contained only 1 case of metastatic carcinoma (Grossniklaus et al.). Up to 1996, 21 cases had been reported. The primaries are listed in table 6.21. Skin melanoma and breast cancer are the most frequent.

Fig.6.10 - Metastasis to the conjunctival surface

Table 6. 21 - Metastases to the Conjunctiva
Primaries Involved
Series of Kiratli + literature

Breast cancer	5 cases
Bronchial cancer	3
Skin Melanoma	7
Stomach cancer	1
Colon cancer	1
Testicle seminoma	1
Larynx	1
Urinary bladder	1
Unknown	1

They are located at the bulbar surface or at the palpebral surface of the eyelid (fig.6.10).

Symptomatology will be obvious: a visible nodule with dilated vessels (red eye), foreign body sensation or tearing. Multiple lesions were present in about half. One noteworthy aspect is that almost all patients have either other ocular metastases such as within the iris and/or widespread systemic metastases, the ocular lesions being frequently part of disseminated disease.

METASTASES to the OPTIC NERVE

Malignant cells can travel from the orbit or the eye to the optic nerve head and occur anywhere along the course of the nerve, including the optical canal. In an autopsy study of 169 secondary optic nerve tumors, metastatic tumors were found in 12% of the cases (Christmas et al.). Metastases to the optic nerve account for less than 2% of the metastatic solid tumors to the eye and orbit (Shields et al.).

Pathways

Three routes will be considered; direct continuous invasion from intraocular tumors or from neighbouring brain tumors or processes such as meningitis carcinomatosa, infiltration by lymphoma and similar processes, and finally the true distant metastases.
True metastatic lesion was assumed to arise from a tumor embols in the central retinal artery, lodging at the cribriform plate due to the narrowing and annulation of the vessel at this site. This theory is, however, not supported, as most presented with a sizeable mass and only a partial venous occlusion without occulsion of the retinal artery. This probably indicates that the tumor originally lodges outside the major vessels and compress them through expansion in size. The nerve head is supplied by branches of the short posterior ciliary arteries, but it is improbable that choroidal lesions will not occur by this pathway.

Table 6.22 - Secondary Optic Nerve Tumors
Classification proposed by Christmas et al. 1991

	Frequency(')
Eye Tumors	79%
Uveal Melanoma	
Retinoblastoma	
Hematopoietic	4.7%"
Leukemia	
Lymphoma	
Myeloma	
Metastatic	12%
Meningeal Carcinomatosis	
Orbital Invasion from Sinus	
Primary Brain Tumor	3.5%

(') from their series of 169 patients

According to Arnold et al., there is a greater likelihood that metastatic cells arriving via the longitudinal nutrient system of the nerve head surrounding the central retinal artery. The tumor will grow forward until restricted by the cribriform plate, presenting with a visible mass.

Christmas et al. have proposed a classification for the different secondary optic nerve tumors (table 6.22). The majority are, in fact, extensions from intra-ocular tumors.

Primaries

A literature review by Arnold et al. in 1981 found only 15 cases from the literature. Mack et al. reported 20 literature cases (table 6.23).

Table 6. 23- Secondary Optic Nerve Tumors
Primaries of true distant metastases
Literature Review by Mack et al. 1997

Bronchus Carcinoma	5 cases
Breast cancer	4
Stomach cancer - GIT	4
Sarcoma	3
Pancreas	1
Prostate	1
Melanoma of skin	1
Carcinoid	1

A type 1 presentation from a bronchial (SCC) cancer was reported by Gallie et al.
Christmas et al. stated in 1991 that a probable total of 142 cases had been reported, including their own 20 cases. Based on the given references, however, this is open to doubt. In our survey we could only find a few bronchial and breast cancer cases in the last decade.
This metastasis is probably underreported as autopsy probably never examines the optic nerve, unless there had been some complaints and the pathologist is interested in.

Symptomatology

Loss of visual acuity in de preceding months is the main presentation.
When examined, most patients show a visible mass on the optic nerve head. At pathology, the metastases seem to involve the parenchyma of the nerve rather than the sheath, but in a few cases it was more within the sheath (Arnold et al.). In many reported cases, there was a varying degree of retinal vascular occlusion due to vascular compression. Early disc hyperemia or tortuous and congested retinal veins were seen at ophthalmo scopy.
Usually the tumor evolves to further retinal vascular occlusion, with rubeosis iridis, neovascular glaucoma and blindness.

METASTASES to the OPTIC DISC

Isolated cases of metastasis to the optic disc have been reported. Only Shield et al. have recently reported on a large series of 30 patients from a consecutive series of 660 patients with metastatic cancer or 4.5%. The primary was unknown in 16 of the 30 patients (table 6.24). Five bronchial cancers in women were revealed by the metastasis. No side preference was observed.

Table 6.24 - Metastasis to the Optic Disc
Primary Tumors according to gender (N=30 patients)
Date of Shields et al. (2000)

Primary	Women (N=24)	Men (N=6)
Breast	13 (1)	0
Bronchus	6 (5)	2
Intestine	1 (1)	0
Kidney	1	0
Prostate	--	1 (1)
Unknown	3 (3)	3 (3)

(-) tumor unknown at presentation

Vision problems were the main symptom, but only three experience severe pain. The authors reported the ophthalmoscopic features observed in these patients. We have tabulated the data in table 6.25.

Table 6.25 - Metastasis to the Optic Disc
Ophthalmoscopic Features (N=30 patients)
Date of Shields et al. (2000)

Centrally located	81%
Eccentric located	19%
Some venous stasis	64%
Color of tumor: white	52%
yellow	32%
flesh pink	16%
Disc tumor presents as nodule	5%
presents as diffuse	26%
Blood vessels crossing on disc	8%
obscured by tumor	23%
Hemorrhage present	13%
Choroidal metastases juxtapapillary	23%
at first visit	16%

The authors have reviewed the literature up to now and could retrieve 16 cases, of which 7 were from a breast cancer.

Table 6. 26 - Ocular Metastases in Children
Literature Review by Endo et al.

	Patient	Eye
Choroid		
Embryonal Carcinoma testis	M04	Right
Neuroblastoma	M03	Left
	F03	??
	F00	Both
Bronchial adenoma	F19	Right
Ewing sarcoma	M26	Right
Colon cancer	M18	??
Thyroid cancer	F09	Right
Congenital fibrosarcoma	M03	Right
Iris		
Neuroblastoma	F00	Right
	F00	Both
	M00	Left
Choroid and Iris		
Hepatoblastoma	F00	Both

(00) = newborn

METASTASIS to the EYE in CHILDREN

Metastatic intra-ocular tumors in children are extremely rare, contrary to the incidence in adults. In the large series, children account for only a few cases. Most are metastases from the typical cancers one encounters in this age group.
Reporting on a neonatal hepatoblastoma presenting with ocular metastases, Endo et al. reviewed the literature and could retrieve only 12 cases, to which their case should be added (table 6.26).
According to the reviewers, metastases to the orbit are not uncommon.

METASTASES to the FACIAL REGION

Metastases to the facial region are commonly named metastases to the head and neck. The various literature reviews and reports sometimes add a different number of specific sites which may or may not be included. Some include skin metastases, salivary gland metastases and jaw metastases. Others only consider the oral cavity and specific sites. We have tried to put some order into them by clasifying them in the following way:

Tumors of the Suprastructure:
- Sinuses: sphenoid, frontal, ethmoid and maxillary
- Nasopharynx
- Nasal Cavity (excluding nose tip)

Tumors of the oral cavity:
- Palate, tongue, tonsilla cheek and/or buccal mucosa, gingiva

Tumors of theNeck:
- Pharynx and Larynx,
- Thyroid cartilage,
- Parathyroid and Thyroid glands.

The tumors of the skin and of the mandibula are discussed in the chapter on soft tissue and bone. Jaw metastases are sometimes difficult to differentiate from gingival metastases.
One particular characteristic is that about 15% of the metastases in this region are first sign or revealing metastases (type 1 metastases).

METASTASES to the SPHENOID SINUS

Metastatic tumors from distant tumors are rare. When compared with the number of other paranasal sinuses, their number accounts for about 20%. They obviously occur through arterial dissemination. Batson's way must also be taken in account as there is a rich venous anastomotic network at the base of the skull near the sinuses. They must be differentiated from neighbou-

ring tumors invading the sphenoid sinus, a much more common occurrence.

Primaries

A literature review in 1991 came up with 27 cases (Andaz et al.) (table 6.27). Prostate is the most frequent one, unlike to the other sinus, as we will discuss later.

Table 6. 27 -Metastases to the Sphenoid Sinus
Primaries Involved
Review by Mickel et al. & Andaz et al.

SupraDiaphragmatic			
Thyroid	5cases		
Breast	3		
Bronchus	8		
Sinus Pyriformis	1		
Gingiva	1		
Salitary Oral gland	1		
InfraDiaphragmatic			
Prostate	8	Rectum	3
Stomach	1	Bone-BoneMarrow	4
Adrenal	1	Urin.Bladder	1
Kidney	4	Testis seminoma	1
Liver	1		

We have added the 7 cases reported by Mickel et al. and the three found by them, but not mentioned in the review by Andaz. We have added those reported by Barrs et al. (1979), making a total of 43 cases. We are not aware of any other case reports since 1991, except Mochimatsu et al. in 1993 reporting a hepatocellular carcinoma metastatic to the sphenoid sinus.
A man with sphenoid metastases from a laryngeal carcinoma treated a few weeks previously, was reported by Keiner et al.

Symptomatology

The symptomatology is no different from that of primary or invading tumors. The signs are related to the proximity of many cranial nerves and the orbit. Diplopia and other problems of vision are common, while pain, headache and neurological syndromes (ophthalmoplegia) are also frequent. Epistaxis is very common, as usual when a renal carcinoma is the primary involved.

Mickel et al. have reported one type 1 metastases revealing a bronchial adenocarcinoma at autopsy.

Diagnosis

The advent of CT has revolutionized imaging of the region, so that any pathology is now detected much earlier than three decades ago. Knowledge of treatment of a previous malignancy is helpful, but the clinician should always be aware of the possibility of such metastases, of course to be differentiated from a primary, in spite of their rarity.

METASTASES to the FRONTAL SINUS

According to Toomey et al., there had been no reports of metastasis to the frontal sinus until their one from an adenocarcinoma of the rectosigmoid. The primary was found only at autopsy (type 1 presentation). It is possible that they were confused with the rare occurring metastasis to the frontal bone, although differential diagnosis was not easy before the advent of CT.

Friedmann et al. mentions a 1905 report by Albrecht of a kidney cancer, another kidney tumor by Van Duyse et al. in 1922 and Mochimatsu et al. in 1993 report an osteogenic sarcoma of the tibia and one hepatocellular carcinoma metastatic to the frontal sinus.
The literature review by Friedman et al. and by Bernstein retrieved 9 cases, 5 from a kidney, 1 thyroid, 1 uterine sarcoma and 1 uterine tumor
We found 6 additional cases in the literature, four from a renal carcinoma, 1 from a breast cancer and one prostate. In the report by Bernstein et al. there was 1 renal cell and one bronchial cancer.
This makes a total of 14 from a renal cell carcinoma of the 23 reported in the literature.

Local supranasal pain seems to be the main presenting symptom.

METASTASES to the ETHMOID SINUS

Many cases are reported together with the other paranasal sinuses such as maxillary and nasal cavity. The literature review by Friedmann et al. revealed 45 sinusal cases, to which they added 10 other cases. We have added the cases reported by Bernstein et al. In both series, only 4 ethmoidal metastases were found: three from a kidney, one from a pancreatic carcinoma and from a stomachal cancer.
The question can be raised as to how far they can be differentiated from those described as metastatic in the nasal cavity, which seems a frequently reported site, especially for renal cell carcinoma. We found 19 reports concerning renal cancer, to which can be added 2 breast cancers, 2 bronchial cancers and 2 malignant melanomas. Mochilmatsu et al. have reported one osteogneic sarcoma of the tibia and one liver cancer metastatic to the ethmoid.

Symptomatology is aspecific. Pain, nasal discharge and nasal obstruction. CT imaging is the mainstay of imaging while a biopsy is needed for definite diagnosis.

METASTASES to the NASAL CAVITY

Several case reports have described patients with metastases to the nasal cavity, but grouped them with those involving the paranasal sinuses. In their review in 1965, Friedmann et al. mention 20 cases, of whom

16 were from a renal cell carcinoma. Bronchial cancer accounted for 2 cases and breast and testicle cancer for one each.
We found 24 references on metastases to the nasal cavity. Half of them concerned indeed renal cell carcinoma. The other reports were about bronchial, brain, liver, testis, uterus (each 1) and two from a choriocarcinoma and from the prostate.
Symptomatology is aspecific: pain, nasal discharge and nasal obstruction. CT-imaging is the mainstay of imaging before a biopsy.

METASTASES to the MAXILLARY SINUS and ANTRUM

The most common site of metastases in the paranasal sinuses is the maxillary sinus.
As from the same reports as mentioned above we found that the renal carcinomas are in the majority (table 6.28). There are a quite high number of testicular carcinomas.
Symptoms are no different from a primary tumor at this site. Pain, nasal discharge and swelling are the most prominent. Epistaxis is a common first sign at that site.
Bouquot et al. have reported on a women aged 80 with a urinary bladder cancer metastatic to the maxillary sinus.

Table 6. 28 - Metastases to the Antrum
Primary Involved, Literature review up to 1985
Modified from Kent et al.

Kidney	20 cases	Breast	8 cases
Testis seminoma	9	Bronchus	5 cases
Uterus NOS	1	Pancreas	1
Stomach	3	Choriocarc	1
Melanoma	3	Adrenal	2
Thyroid	1	Colon	1

METASTASES to the NASOPHARYNX

These occur very rarely. Only about 20 documented cases have been reported (table 6.29).

Table 6. 29 - Metastases to the Nasopharynx
Primary tumors
Based on Review by MacKay

Melanoma	9
Kidney	4
Bronchus	1
Breast	1
Colon	1
Cervix Uteri	1

Hematogenous route and Batson's plexus constitute probably the main pathways.
Malignant melanoma is the main source, but renal cell cancers are the main epithelial source.
A male patient with a pancreatic carcinoma was reported in 1989 by Bouquot et al.
Symptomatology is no different from a primary nasopharyngeal cancer, also trelatively rather rare in our region.
Nasopharyngoscopy, biopsy and CT are the mainstay of diagnosis.

METASTASES to the ORAL CAVITY

Metastatic involvement of the different sites within the oral cavity is uncommon in daily oncology practice. All the cases that have been reported have been as isolated reports or small series.
It would appear that there are some preferred sites. The gingiva is involved in about half of the cases and one quarter are metastases in the tongue.
The most recent review of the cases reported in the English literature is by Hirshberg et al. in 1994. They collected 390 cases, but there was no breakdown into anatomic sites. Nishimura et al. collected 41 cases deivided up as in table 6.30.

Table 6.30 - Metastases to the Oral Cavity
Anatomic Sites involved
Data of Nishimura et al. 1982

Site	
Gingiva Upper	20
Gingiva Lower	6
Maxilla	2
Mandible	17
Buccal Mucosa	1

Several series have reported on the primaries where these metastases originated. Five series are grouped in table, totalling 371 cases (table 6.31). The series are however dissimilar and have certainly some referral bias.

Table 6.31 - Metastases to the Oral Cavity
Primary Involved (N=371) 5 literature series (°)

Above Diaphragm (203 cases or 54.7%)			
Bronchus	47 (12.6%)		
Eye (retinobl.)	4		
Thyroid	60 (16.2%)		
Breast	85 (23.0%)		
Lip (')	7		
InfraDiaphragmatic			
Uterus	16	Stomach	14
Kidney	44	Liver	4
Intestine	15	Adrenal	1
Prostate	18	Ovary	7
Skin Melanoma	14	Others	21

(°) Castigliano et al. 1954 (N=176); Clausen et al. 1963 (N=97); Meyer et al.1965 (N=25); MacDaniel et al. 1971 (N=32); Nishimura et al; 1982 (N=41)

METASTASES to the BUCCAL MUCOSA

Although mentioned in several series of oral metastases, dedicated reports are absent from the literature. Of the 157 reviewed cases of oral metasta-ses, Hirshberg mentions only 2 cases or 1.3%.

METASTASES to the TONGUE

Metastases to the tongue are rare. In the large autopsy series of Abrams, only 1 case was recorded, while Willis had 1 in 500. Weitzner et al. reported one case, a solitary metastasis from a stomach cancer, in 745 autopsies of oncology patients.
In 1973, Zegarelli et al. reported 12 cases from a very large autopsy series, 6881 patients, or 1.7/1000. Five of them were from a malignant melanoma.
The literature was reviewed in 1992 by Baden et al. (table 6.32). More than two thirds involved males.

Table 6. 32 - Metastases to the Tongue
Primary Cancers
Review by Baden et al. 1992

Skin (melanoma)	13 (17%)
SupraDiaphragmatic	
Pharynx	1
Eye	1
Bronchus	16 (21%)
Breast	6
Esophagus	4
Brachialis muscle	1
InfraDiaphragmatic	
Kidney	16 (21%)
Pancreas	2
Colon	5
Uterus	3
Testis	2
Adrenal, Prostate, Fibula (sarcoma) each 1	

Pathways
As with all oral and head and neck sites, arterial, venous and Batson route explain their occurence. Their rarity is explained by the fact that muscles do not appear as good receptors for metastases (see Chapter 7).

Table 6.33 - Metastases to the Tongue
Site Involved (N=56)
Data of Baden et al.

Base Posterior	27 or 48%
Lateral Border	14 or 25%
Dorsum	10 or 18%
Tip of tongue	5 or 9%

Pathology

Although Zegarelli found more tumors in the base, the review by Baden et al. concluded that there was an equal distribution between base and mobile part. This is probably not significant in any way (table 6.33).
It is striking that 10 of the 77 cases, or 13%, are sarcomas of different types.
The tongue was the first presentation of an unknown tumor in 10 cases (13%). It is noteworthy that in 47 cases (61%) it was the first metastasis of a previously treated tumor.

METASTASES to the PALATE

This is a rarely reported site for metastases. Of the 157 reviewed cases of oral metastases, Hirshberg mentions only 7 cases or 4.5%.
We are aware of only 7 other reports. They consist each of 1 case from a carcinoid, a stomach cancer, a skin melanoma, a sarcoma and two from a kidney cancer, of whom one metastasized to the uvula.
Brochériou et al. reported a type 1 metastases from a bronchial cancer.
Patients report a progressive swelling in the palate.

METASTASES to the GINGIVA

This is the most frequent site of metastases within the oral cavity. Of the 157 reviewed cases of oral metastases, Hirshberg mentions 86 cases or 55.1%.
A bibliometric survey shows that of the 51 known reports, the liver was the primary in 7 reports and breast and kidney each 6 times.
Several are type 1 metastases.
The primaries as retrieved by Hirschberg et al. are in table 6.34. Since their report, there have been reports concerning pancreatic, rectal and testicular carcinoma. Carcinoid, chondrosarcoma, Meckel skin tumor, Ewing sarcoma, esophageal and one adenoid cystic carcinoma of the trachea were some of the unusual cases.

Table 6. 34 - Metastases to the Gingiva
Primaries as Retrieved by Hirschberg et al. 1993

Bronchus	22 cases	Stomach	2cases
Kidney	6	Esophagus	2
Skin	6	Pancreas	1
Breast	5	Eye (retinoblast)	1
Fem.Genitalia	2	Muscle	1
Colon Rectum	4	Urinary Bladder	1

One gingival tumor was the first metastasis of an adenoid cystic carcinoma of the trachea, resected 17 years previously in a man of 58 (Dahl et al.).

Symptomatology is marked by a progressive swelling of the gingiva, with progressive ulceration and bleeding. Differential diagnosis with epulis and other more common pathologies is mandatory. Final diagnosis must be obtained by biopsy.

METASTASES to the TONSIL

Of all the oral metastases, this is one of the rarest sites involved. Fernandez-Acenero et al. cite 70 reported cases, mainly melanoma, breast, bronchial and stomachal cancers, but also from kidney and seminoma. Data are not provided. They add one case from a melanoma and one from an hepatocellular carcinoma.
A women aged 77 with papillary carcinoma of the thyroid was reported by Mochimatsu et al. One case (M62) from a pancreatic carcinoma was reported (Feleppa et al.). The most extensive review was published in 1979 by Brownson et al. (table 6.35)

Table 6.35 - Metastases to the Tonsils
Literature Review 1979 (Brownson et al.)

Primary		Bilateral
Stomach	5 cases	40%
Seminoma Testis	6 cases	40%
Breast	11 cases	33
Bronchus	12	17
Melanoma	13	46
Kidney	14	8
Rectum	2	
Gallbladder	2	

and 1 case of
choriocarcinoma, prostate, sinus pyriformis,
bronchus (adenocarcinoma), contralateral tonsil,

Bilateral involvement is not rare, is even common for melanoma (46%) and rare for hypernephroma (8%). In the unilateral cases, the left tonsil is apparently more involved in the stomach and breast, and still more in melanoma. In hypernephroma there are more metastases at the right side.
The hematogenous route is the most probable.
Diagnosis will be directed by the dysphagia and otalgia of the patients, the clinical inspection and biopsy and knowledge of a previous neoplasm.

METASTASES to the LARYNX

Metastatic involvement of the larynx from distant neoplasms is rare. According to Nicolai et al., up to 1996 'only' 143 were reported.
Literature data show that metastatic tumors account for 0.09 to 0.4% of all laryngeal tumors.

Pathways

The rarity of those metastases can be explained by the terminal location of the organ in the vascular and lymphatic circulation. The wide angulation of the art. thyroidea superior can also be considered a factor preventing the arrival of malignant cells.
Three routes have been proposed:

1. The classic hematogenous route along the carotid artery and its branches;
2. The vertebral venous plexus of Batson;
3. A direct lymphogenous route of afferent lymphatic vessels originating from the thoracic duct to mediastinal, intercostal and left supraclavicular nodes. Some authorsclaim to have documented a connection between the subglottic region and the subclavian nodes.

Not to be considered as a metastasis is the common invasion of laryngeal cartilage and larynx by contiguous neoplasms, a not unusual occurrence in thyroid carcinoma,

Primaries

The most recent complete literature review dates from 1988 (table 6.36). The majority, about one third of the cases, are from a malignant melanoma. Of the 146 cases, 32% are from infradiaphragmatic tumors.

Table 6.36 - Metastases to the Larynx
Literature Review by Ferlito et al. (')

Supra Diaphragmatic		Infra Diaphragmatic	
Nasopharynx	2	Kidney	18
Jaw (sarcoma)	1	Prostate	9
Breast	12	Stomach	3
Trachea	1	Colon	6
Bronchus	12	Pancreas	2
Mediastinum (sarc)	1	Testis	2
Esophagus	1	Cervix Uteri	2
		Ovary	2
Other		Gallbladder	1
Skin Melanoma	44	Adrenal	1
Other Melanoma	3	Retroperitoneal	1
Bone	3		
Esthesioneurobl.	1		
Angiosarcoma	1		

(') including 10 additional cases (review by Nicolai)

Pathology

Reviewing the literature, Ferlito et al. found that 38.2% of the metastases were located in the supraglottis, 5.3% in the vocal cord and 18.4% in the subglottis. In 35.5%, the whole larynx seemed to be diffusely involved. In 2.6%, the metastasis was located in the retrolaryngeal space.
The macroscopic aspects should be enough to raise suspicion, since metastatic lesions are fungating, polypoidal or nodular but covered with normal mucosa.
Biopsy is not easy because the lesions are commonly submucosal. Bleeding is frequently a surprising event.
The histology of the metastases usually correlates with the primary, and will give rise to a definite diagnosis.

Symptomatology

The signs and symptoms of laryngeal invasion or metastases are no different from the more common primary laryngeal cancers. Dysphagia, hoarseness, and referred ear pain are wellknown. More so than in the primary tumors, hemoptysis is not uncommon, probably due to the high vascularisation of the meta-

stases.
Most authors do not make a distinction between metastases in the larynx proper and those in the cartilage bone. The majority will in the larynx. Metastases have been observed within the bone marrow of the thyroid and cricoid cartilage (see farther).

Diagnosis

The definite diagnosis is usually obtained from a biopsy, but one should beware of the high risk for hemorrhagic incidents. These patients have usually other metastases.

METASTASES to the PHARYNX

This is a very rarely reported metastatic site.
We found one case report implicating a breast cancer and two a malignant melanoma.

METASTASES to the THYROID CARTILAGE

Friedmann found 5 cases from breast cancer reported by Ehrlich (1954) and another by Ellis et al.(1957).
The former studied the laryngeal cartilage of patients with generalized bone metastases and found that 22% of them had involvement of the cartilage.
It would seem that as long as the cartilage has not transformed to bone, metastases cannot settle within it.
A number of mammary and bronchial cancers have been reported (short review by Glanz et al.). In a series of head and neck metastases from urogenital cancers, one patient was reported by Hessan et al. as first sign from a prostate cancer.
We are aware of one man aged 40, presenting with pain in the larynx, as first sign of a metastatic urinary bladder carcinoma. A case of metastasis from a rectal carcinoma has been recently reported by Bosca et al.

METASTASES to the PARATHYROID GLAND

We are aware of only two studies. One study dates back to 1911 and includes two cases.
A prospective study of 160 consecutive oncology patients revealed parathyroid metastases in 19 cases or 11.9% (Horwitz et al.). A retrospective study at the same institution revealed forty cases in 750 necropsies or 5.3%. The different primary tumors for both groups are listed in table 6.37.

It seems that some cases were reported in the literature prior to World War II, but these were not available to us. We are not aware of more recent reports. As far as can be deduced from the literature review by Horwitz, most were from a breast cancer (50%), but at least one was from a prostatic cancer.

Table 6.37 - Metastases to the Parathyroid Gland
Primaries involved
Report of Horwitz et al. 1972

Breast	24 cases	Kidney	1
Leukemia	10	Prostate	1
Skin melanoma	8	Stomach	1
Bronchus	3	SalivaryGlands	1
Lymphoma	3	Tongue	1
Sarcomas	2	Testis	1
Bone Marrow	2	Thymoma	1

In a series of head and neck metastases from urogenital cancers, one patient was reported from a urinary bladder cancer by Hessan et al.
Obviously, the detection of parathyroid metastases requires a particular dedication and extensive microscopy studies.

The destruction of all the parathyroid should lead to hypocalcemia, a possible feature of this metastasis, that must be differentiated from other causes of hypocalcemia.
The absence of any report in the modern literature is strange and probably due to a lack of interest.

METASTASES to the THYROID GLAND

The thyroid gland is probably the most frequently involved site of those grouped here in this chapter on Head and Neck metastases.
Usually considered uncommon, autopsy series with microscopic studies have concluded that there is a much higher incidence than is clinically suspected. However, in these studies the variability of the data will depend on the diligence of the pathologist.
When the incidence of metastases is related to vascular output, thyroid metastases are second only to those in the adrenal gland.
Every oncologist will meet this clinical picture at least several times in his practice. A thyroid nodule in patients with known neoplasms will present a challenging diagnosis.

Autopsy Data

In most autopsy series, breast and bronchial cancers are the two most frequent primaries involved, while in clinical series renal cell cancers are the most frequent. This may be explained by the slower growth of breast and bronchial cancer in the thyroid (table 6.38).

Incidence

There are differences in the relative frequency of the involved primaries, when clinical series are compared with autopsy series. Affirmative data were collected and reviewed by Froidevaux et al. in 1977. More recent literature is pending (table 6.39).

Table 6.38 - Metastases to the Thyroid Gland
Incidence data from Autopsy series

Author	N	Percent with meta
Wills 1931	170	5.2
Rice 1934	89	10.1 (')
Mortensen 1956	467	3.9 (')
Thorpe 1954	200	2.0
Shimaoka 1961	1980	8.6 (')
Silverberg 1966	62	24.2
Berge 1977	7732	2.8
Abrams 1950	1000	1.9

(') included lymphoma patients
(°) only epithelial tumors

Table 6. 39 - Metastases to the Thyroid Gland
Comparative data in Clinical and Autopsy series
collected by Froidevaux et al. 1977

Primary	Autopsy N=10000 538 metastases	Clinical N=not stated 91 metastases
Breast cancer	20%	11
Bronchus	16	12
Melanoma	15	4
Lymphoma	16	none
Kidney	9	**53%**
GITract	7	12
Uterus	7	1
Pancreas	3	none
Skin cancers	3	2
Liver-Bile duct	1	1
Other	3	4

Although metastatic thyroid cancers are about 10 times more frequent than primary thyroid cancers, they are not a serious clinical problem, as about half of them are not found at clinical examination, and are asymptomatic. The problem rises, however, when they are the first symptom or sign of an unknown primary elsewhere, about one third of the thyroid metastases, as we will see later. We are not aware of any reports iabout the occurrence in children.

Type 1 Metastases

A particular feature of metastases in the thyroid is the presentation with a tumor nodule before the primary concerned is known. From the literature series (no case reports) we retrieved several data allowing to an estimation of the global incidence (about 34% (table 6.41).

Pathology

In spite of the large numbers of reports, none has provided adequate pathology. Only Shimaoka et al. had adequate data (table 6.40).

Table 6.40 - Metastases to the Thyroid Gland
Pathology Data in 188 lesions
Data of Shimaoka et al. 1962

Diagnosis only at Microscopy		109 (58%)
Diagnosis at Macroscopy	79	
Aspect Infiltrative	28	
Nodular mass	51	
Multiple	34	
Single multi-nodule	2	
Solitary	15	
Size (of those recorded, N=61)		
less than 1 cm	20	
1.0 - 2.0	16	
more than 2 cm	25 (41%)	

More than half of the metastases were found only at microscopy, stressing the need for adequate pathology studies to detect occult metastases.
Quite a number will have a large size.

Table 6.41 - Malignant neoplasms presenting First in the Thyroid (type 1- metastases)
Literature Review by the author of small series - (case reports not included)

Author - Year	N	
Thomson 1975	1/2	Colon 1
Hagenauer 1980	3/5	Esophagus 1, Colon, 1, Bronchus 1.
Gazel 1982	1/2	Testis 1
LaMeir 1982	1/4	Kidney 1
Czech 1982	2/12	two adenocarcinoma of the bronchus
Ivy 1984	8/30	Bronchus 3, Kidney 2, Sarcoma 1, Pancreas 1, Esophagus 1.
MacCabe 1985	4/17	Esophagus 2, Bronchus 2.
Schröder 1987	19/25	insufficient data, 3/8 of the kidney cancers
Rigaud 1987	2/6	Bronchus 1, Breast 1
Schmid 1991	14/25	
VanderSangen 1993	4/16	Bronchus 2, Larynx (??) 2 (invasion?)
Michelot 1995	16 cases:	Bronchus 8, Stomach 4, Larynx 1, Melanoma 1, Prostate 1, AML 1.
Lam 1998		18/79 (23%) Bronchus 9, Lymphoma 3, Breast 2 + Bone, Endometrium, Nasopharynx and colon, each 1
TOTAL		**77/223 = 34.5%**
Edmonds 1978	one breast cancer with hyperthroidism	
Bischof 1999	one case of small cell bronchus	

Symptomatology

The presentation in these patienst is invariably a growing tumor within the thyroid gland, reported as recently noted.
Hyperthyroidism is ararely associated with a metastasis. The infiltration and destruction of the thyroid tissue by the invading metastases has been demonstrated to provoke an excessive release of thyroid hormones.
A case of pancreatic (Eriksson) and one of breast cancer (Edmonds) have been published. The other concerned a malignant lymphoma.

Diagnosis

Clinical examination must be completed with Ultrasonography. This will usually not lead to a specific diagnosis so that fine needle cytology or biopsy is to be recommended. Mostly US.graphy recognizes a heterogenous structure, very rarely cystic or calcified foci. The lesions are echo-poor with sharp borders. The zone of demarkation is abrupt. It can more readily detect lesions smaller than the cold lesions detected with radionuclide scintigraphy.

According to Ahuya et al., thyroid metastases involve either an entire lobe or predominantly the lower poles.

Synopsis

Fig.6.11 illustrates the preferential head and neck sites according to the primaries most frequently involved.

Metastatic SITE	**Primary Most Frequently Involved**
Salivary Gland	
Parotid Gland	Skin Melanoma
Ophthalmic	
Orbit	Breast cancer
Iris	Breast Cancer
Chroid	Breast cancer
Retina	Skin Melanoma
Vitreous	Skin Melanoma
Conjunctivae	Skin Melanoma
Optic Nerve	Bronchus carcinoma
Head and Neck	
Sphenoid Sinus	Bronchus cancer
Frontal Sinus	Kidney cancer
Ethmoid Sinus	Kidney cancer
Nasal Cavity	Kidney cancer
Maxillary Antrum	Kidney cancer
Nasopharynx	Skin Melanoma
Tongue	Bronchial Cancer Kidney
Gingiva	Hepatocellular Carcinoma
Tonsil	Skin Melanoma
Larynx	Skin Melanoma
Parathyroid	Breast cancer
Thyroid	Kidney Cancer

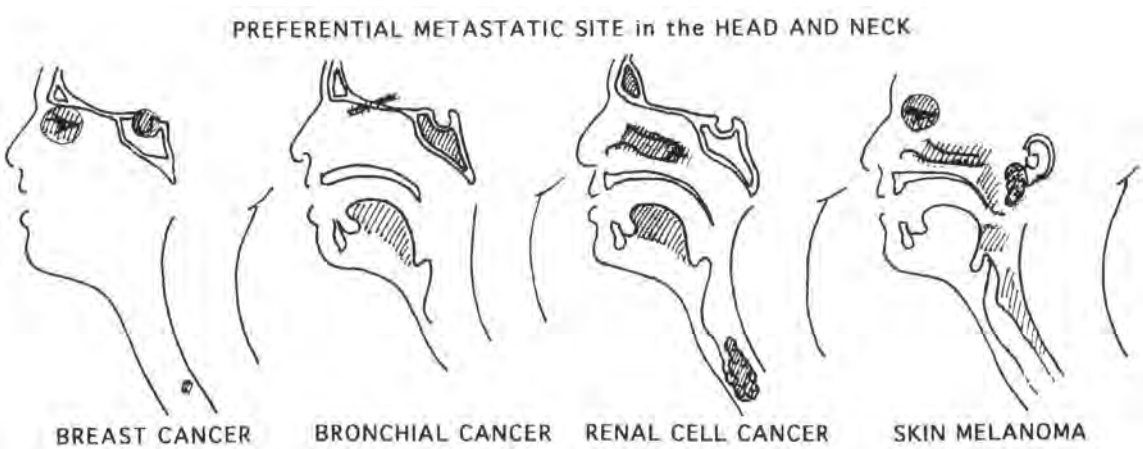

Fig. 6.11 - Preferred sites for head and neck metastases according to the primary

References

Caution: References are given for documentary purposes. Not all have been reviewed or used in the redaction of the text. We do not claim completeness of data. The references are as much as possible grouped per subject heading.

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7
METASTASES
to the SKIN, SOFT-TISSUES and BONE

In this chapter we have grouped what can be called 'non-organic' metastases. We will discuss here the metastases to the skin and subcutaneous tissues, the metastases to the muscles, the vascular tumor emboli, bone marrow and bone metastases, the 'non-regional' lymph node metastases and the metastases within benign and malignant tumors.

METASTASES to the SKIN

These visible metastases onot only have an esthetic impact but have also an important prognostic significance. Their diagnosis is not always evident as they can present under various forms, masquerading as other skin diseases.
Recognizing skin metastases is important as they can appear in several clinical forms not immediately evident as their metastatic nature and are quite similar to to other more common skin disease. The recognition is poarticularly important when they appear first in a patient who are unknown to have a malignant neoplasm anywhere.

Pathways

Knowledge of the pathways for metastatic skin disease is important as far as histologic differentiation is possible.
As with many metastases discussed there are different mechanisms (table 7.1), and only a few can be considered true metastases. The differentiation is not always made in the literature reports and reviews.
Continuous extension of the tumor along skin lymphatics or fasciae is a common feature of breast cancer. Malignant melanoma also has this characteristic local spread. Many authors consider the thoracal spread of breast cancer as a form of skin metastases, but the lymphangitic extension is, in fact, more a contiguous or continuous spread. Isolated noduli can well be regarded as 'true' though local metastases.

Table 7.1 - Metastases to the Skin
Pathways - Mechanisms

1. Continuous extension of the tumor along skin lymphatics or fasciae;
2. Direct invasion of a subcutaneous tumor ;
3. Hematogenous spread;
4. Regional metameric spread;
5. Implantation of tumor cells within surgical scars.

Any subcutaneous tumor can invade the skin directly. This is not unusual in far-advanced lymph node involvement, some salivary gland carcinomas and sarcomas underlying the skin. These can certainly not be considered true skin metastases.
Metastases in the skin at a some distance and without continuous 'anatomy' can occur after hematogenous spread. They are the true metastases. The vertebral venous system (Batson) has probably also a role in vascular dissemination.

Implantation of tumor cells within surgical scars is a dreaded complication. In modern contexts they can be seen in the needle track of pleural and other inva-sive procedures and most recently they have repeatedly been reported in the trocar site after laparoscopic or

other endoscopic surgeries.

Primaries

The propensity for metastasis to the skin varies from one primary to another.

Table 7.2 - Metastases to the Skin
Primaries involved and relative frequency
Modified from data of Lookingbill et al. 1993

Primary	N	Nwith	%Remote(')
Melanoma	172	68	39.5%
Breast	707	71	10.0
Head-Neck	221	17	7.6
Bronchus	802	19	2.3
Esophagus	35	3	8.5
Stomach	147	1	0.7
Pancreas	107	1	0.9
Urinary Bladder	85	5	5.8
Gallbladder ducts	59	0	0 (*)
Kidney	130	4	3.0
Rectum Colon	413	7	1.7
Ovary	249	4	1.6
Endometrium	183	3	1.6
Uterine Cervix	195	2	1.0
Prostate Testis	220	0	0
Endocrine	24	3	12.5
Unknown	271	20	7.3
TOTAL	4020	227	5.6%

(') all patients with remote skin metastases
(*) including liver tumors.

The best data we found in the literature are those from Lookingbill et al. on a cohort of 4,020 oncology patients. The overall incidence at any time during the clinical evolution was 10.4%. However, the authors included any breast cancer and melanoma with skin involvement, so this value is highly skewed.
Eliminating the metastases registered as 'local' make the incidence 5.6% (table 7.2), which seems to be a more appropriate figure. Data from autopsies more or less corroborate this figure (table 7.3).

Table 7. 3 - Metastases to the Skin
Incidence data from large series
Modified from Krumerman et a l. 1977

Author	N	With skin M	Percent
Gates 1937	2,031	43	2.1
Abrams1950	1,000	44	4.4
Leu 1964	1,357	34	2.5
Reingold 1966	2,300	32	1.3
Willis 1967	424	4	1.0

The reliability of the data on the incidence of skin metastases will de-pend on the thoroughness of autopsy methodology.

Anatomical Sites

There is a good parallelism between the location of the primary tumor and the sites of the skin metastases allowing the conclusion that these metastases have predominantly taken a lymphatic route, at least when they occur within the same body segment.
However, not all skin sites are equally involved. The classic data from Brownstein et al. concerning male patients, are in table 7.4.
From the table, it will be seen that one third of the skin metastases from bronchial cancer are at the chest. For rectocolic tumors 85%, for stomachal 60% of the metastases are within the abdomen. Almost all skin metastases of Head and Neck tumors are within scalp or face and neck. These data point towards a kind of segmental distribution of skin metastases. One explanation at least for the infradiaphragmatic tumors, is some sort of lymphatic reflux through some central blockade (fig.7.5).

Table 7.4 - Skin Metastases in MEN
Distribution according to primary and Site of Metastases
Data of Brownstein et al. 1972

Primary Tumor	Scalp	Face	Neck	Upper extremities	Chest	Abdomen	Back	Pelvis	Lower extremities	Multiple sites	Total
Lung	12	6	10	6	39	16	17	2	3	6	117
Large intestine	1	1	2	4	4	40	3	33	1	1	90
Melanoma	1	4	3	10	15	4	10	3	11	1	62
Oral cavity	0	12	41	1	1	0	0	0	1	1	57
Kidney	5	6	1	4	3	4	3	1	2	0	29
Stomach	1	1	2	1	4	16	1	0	0	2	28
Esophagus	0	3	4	0	3	1	3	1	0	0	15
Sarcoma	1	3	2	0	3	2	2	1	0	1	15
Other	1	5	10	3	15	23	2	4	1	5	69
TOTAL	22	41	75	29	87	106	41	45	19	17	482

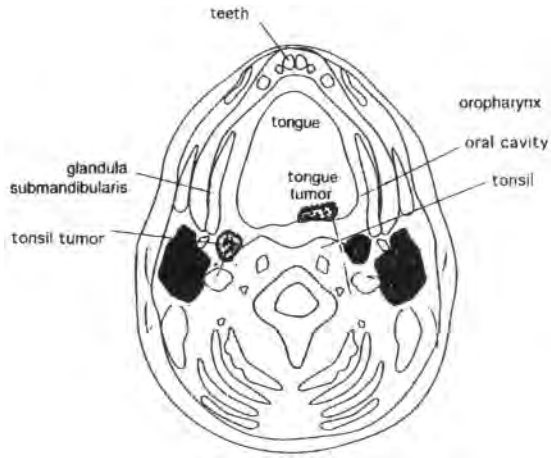


Fig.7.1- Hypothetical pathways of tumor spread explaining the segmental occurrence of skin metastases for head and neck tumors.

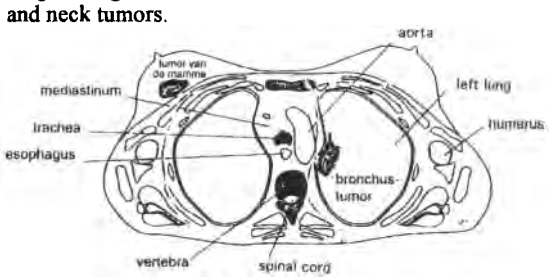


Fig.7.2 - Hypothetical pathways of tumor spread explaining the segmental occurrence of skin metastases for thoracal tumors.

The data for women show a similar trend (not shown). Almost all tumors of the uterine cervix and ovary have skin metastases within the abdominal wall. The particular situation of breast cancer patients will not be discussed further here.

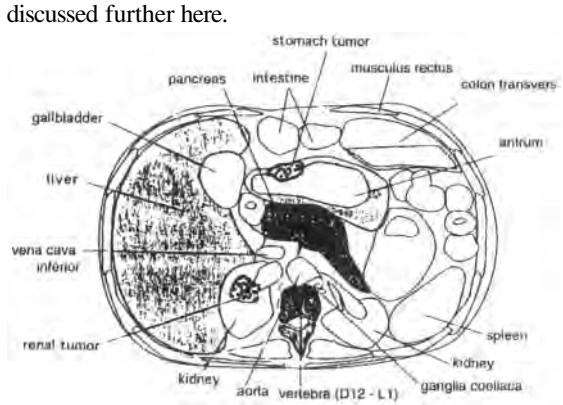


Fig.7.3 - Possible alternate route of tumor spread explaining the segmental occurrence of skin metastases for abdominal tumors.

Type 1 Metastases

Quite a number of the skin metastases present as first sign or symptom of a hitherto unknown malignancy. According to the data from Brownstein et al., 27% of the skin metastases in male patients were from an unknown primary (table 7.5). In women it accounts for only 6.1%. The concerned primaries are shown in table, together with the sites of presentation for men or for women (table 7.6).

Table 7.5 - Type 1- Skin Metastases in MEN
Primary and Site of presentation
Data of Brownstein et al.1972

Primary	N	Head	Chest	Abd	U.Ext	L.Ex
Bronchus	72	18	20	25	4	2
Kidney	15	7	1	3	2	2
Stomach	9	2	1	6	0	0
Pancreas	9	1	3	4	0	0
Colon	5	0	2	2	1	0

(°) those not included had multiple sites
U.ext.: upper extremity; L.EX.: lower extremity

Table 7. 6 - Type 1- Skin Metastases in WOMEN
Primary and Site of presentation
Data of Brownstein et al.1972

Primary	N	Chest	Abd	U.Ext
Breast	4	4	0	0
Ovary	4	0	4	0
Bronchus	3	1	1	1
Colon	1	0	1	0
Kidney	1	1	0	0
Stomach	1	0	1	0
Pancreas	1	0	1	0

Many case reports highlighting the first presentation have been reported in the literature, mainly in dermatology journals.

Clinical Pathology

Most cutaneous metastases present as nonspecific painless dermal or subcutaneous nodules with intact overlying epidermis. The color can be flesh, pink, violaceous or brownish black. At palpation they are usually quite hard.
Most are solitary, some are multiple and some are multiple small papules numbering hundreds. Other present as large sclerotic plaques.
Cutaneous metastases can ulcerate but many can grow out to a few centimeters in height.

Rare metastatic types are zosteriform, unilateral and along one neuromere types.
Epidermotropic metastases present as small hemorhagic superficial vesicles. Paget's disease has been considered as being of that type.
Another type described is botryoid, growing like a cluster of grapes. Alopecia neoplastica is rare form occurring in the scalp (see further).
Other presentations have been described, and sometimes difficult to differentiate from other skin diseases (table 7.7).

Table 7. 7 - Cutaneous Metastases Simulating other Skin Diseases Modified from Schwartz

Simulation of	Primary
Blueberry Muffin Baby (viral)	Neuroblastoma
Multiple Cylindromas	Prostate
Large Sebaceous Cysts	Prostate
Pyogenic Granuloma	Kidney
Kaposi's sarcoma	Kidney
Alopecia Areata	Breast
Lymphangiomas	Breast (bronchus)
Morphea	Breast (stomach) (bronchus, mixed)
Erysipelas	Breast, inflamm.
Chancre	Lymphoma Urothelial cancers
Gumma	Lymphoma

Teleangiectatic carcinoma was first described by Weber in 1933, and since then has been called Parkes-Weber syndrome. This is a rare condition appearing usually in breast cancer, but has also been described in other cancers (Zanca et al.).

Histology

At histology, most of the metastases present with the features of the primary, allowing either first diagnosis or confirma-tion of the diagnosis of metastases.
Most difficulties occur with atypic or undifferentiated epithelial (adeno) carcinomas
If not immediately conclusive, immunohistochemistry can certainly be very helpful, but will not be discussed further here.

Diagnosis

Fine needle cytology or biopsy is an suitable diagnostic step. Surgical excision can be considered for painful or hindering metastases, allowing simultaneous histology studies.
Any fast-growing recent skin nodule in a patient with a known oncology past should be considered as malignant unless proven otherwise.
Experienced oncologists are unlikely to miss the diagnosis.

Zosteriform Metastases

Skin metastases following a segmental dermatomal distribution zosteriform as mimicking herpes zoster have been describedas occurring in a small number of cases.
Jaworsky et al. have hypothesized that this particular distribution is caused by peri- or neural spread from a metastatic process within the dorsal ganglion. Hematogenous metastases in the dorsal ganglion may occur when the vascular endothelium of the dorsal root ganglia is fenestrated and provides no blood/ganglion barrier (Matarasso et al.).
Up to 1998 only 14 cases had been reported. Different primaries were involved, none having and none a particular propensity (table 7.8). At least one type 1 presentation has been reported. It concerned a breast cancer in a 62year-old women (Heckman et al.).

Table 7. 8 - Zosteriform Skin Metastases Primaries Involved (Literature review by the author)

Breast Cancer	3 cases
Prostate cancer	3 cases
Bronchus (adenocarcinoma)	2
Mal.Melanoma	2
Renal pelvis	1
Colon rectum	1
Urinary Bladder	1
Unknown	1

Diagnosis is not easy in view of the mimicking aspects. Herpes zoster is also a common complication of advanced cancers. Non-response to classic treatment should give rise to the suspicion, and biopsywill be indicated.

PARTICULAR SITES

A number of particular sites have received special attention in the literature, either because of their rarity or because of other characteristics.
We thought it wort while to discuss the following sites:

- the scalp
- the nose tip
- the eyelids
- the skin of the lips
- the umbilicus, better known as Sister Mary-Joseph's nodule

METASTASES to the SCALP

The scalp is not an unusual site for metastatic skin cancer. This site is easily brought to the attention of the patient and it is easy to discover. Statistical studies state that it accounts for 4 to 5% of all skin metastases.

A few series have been reported, including those of Dreizen et al. in 1991 from an oncology center. Strange is the absence of breast cancer, though in the series of Christeler it accounted for almost half of the 13 cases (table 7.9). The long interval between diagnosis of the primary and the occurence of the scalp metastasis is striking.

In a series of 34 patients with bronchial cancer and skin metastases, 5 or 14% (3 from an adenocarcinoma) had a scalp localisation (Terashima et al.). Reviewing the literature, we also found case reports from rectum, colon, prostate, endometrium, cervix uteri, thyroid, testis, mesothelioma of the pleura and sarcomas. A few were reported as type 1 metastase,s particularly from bronchial cancers.

Table 7.9 - Metastases to the Scalp
Data from two literature series

Christeler 1980		Dreizen et al. 1991	
Breast cancer	7	Bronchus(')	28
Kidney	1	Salivary Gland	2
Thyroid	1	Uterus	1
Larynx	1	Adrenal	1
Stomach	1	Esophagus	1
Liver (?)	1	Sarcoma	1
Unknown	1	Leukemia-Lymphoma	15

One particular form of skin metastases in the scalp is alopecia neoplastica. It can simulate other forms of alopecia and is a rare form of skin metastasis.
We found 8 references and all concerned breast cancer.
It initially appears as single or multiple areas of scarring alopecia. At palpation elevation of the zone is relatively slight but enough to allow biopsy.
Histology demonstrates metastatic cells within a dense collagenous stroma with loss of the pilo-sebaceous units.

Fig.7.4 - Typical aspect of hypertrophic growth of metastasis at the nose-tip, commonly called 'clown nose'.

METASTASES to the NOSE TIP

This unusual site is not rare in bronchogenic cancer. It is a clearly a hematogenous metastasis. It must be differentiated from rhinophyma, a hypertrophy of the nose with follicular dilatation resulting from hyperplasia of sebaceous glands with fibrosis and increased vascularity.
Whre the growth is pronounced, it has been described as a 'clown-nose' (fig.7.4).
We found 9 references concerning this site, of which 7 involved cases of bronchial cancers. Two were even type 1 or revealing metastases. The others concerned breast and larynx cases.

METASTASES to the EYELID

This metastatic site is discussed in the chapter on ophthalmic metastases (Chapter 6).

Cutaneous Metastases in Children

In children cutaneous metastases follow the pattern of tumors common to that age group. The most frequent primary leading to cutaneous metastases is leukemia accounting for 30%, while neuroblastoma is responsible for 7% of the observed metastases. Lymphoma causes a further 10%, while the other 50% will probably be due to diferent sarcomas, epithelial tumors and melanomas (Mather-Wiese et al.).

METASTASES to the LIP

This is apparently a rarely reported metastatic site. We are aware of only two cases reported, one from a breast cancer and one from a bronchial cancer (upper lip).

METASTASES to the UMBILICUS

Metastases to the umbilicus constitute an oncologic curiosity. The diagnosis is probably missed on many occasions. The eponym 'Sister Mary-Joseph's nodule' honors the assistant to Doctor Mayo who pointed out that site was being frequently involved in malignancies of the abdomen.
It has been stated that 10% of the metastases in the abdominal wall are in the umbilicus.
The first report was from Walshe in 1846, and was a review of the reports in the mortuary registers of Paris.

Pathways

In view of the anatomical relationship of the umbilicus with different vascular and embryologic structures, the umbilicus is at a crossroad of various pathways involved in a metastatic process.
Several pathways have been examined:
- Propagation through lymp channels;
- Propagation via a venous network;
- Propagation by contiguous extension;
- Propagation through embryologic remnants.

The umbilicus has an important lymphatic drainage system. There are connections between the peri-umbilical skin and a deep network, or the para-aortic, the external iliac and along the mammaria interna (internal thoracic). There is also a connection with a more superficial network, the axillary and the inguinal lymph nodes. It is thus situated at the crossroads of different routes draining different parts of the abdomen and thorax.

Venous drainage occurs through a network radiating to

the axillary vein, above via the lateral thoracic and femoral vein, and below via the superficial epigastric vein. The venous network of Batson, the epidural, the perivertebral and thoraco-abdominal wall, the veins of the head and neck and the veins of the vertebral column, are connected with the veins of the abdominal wall centered at the umbilicus (fig.7.5).

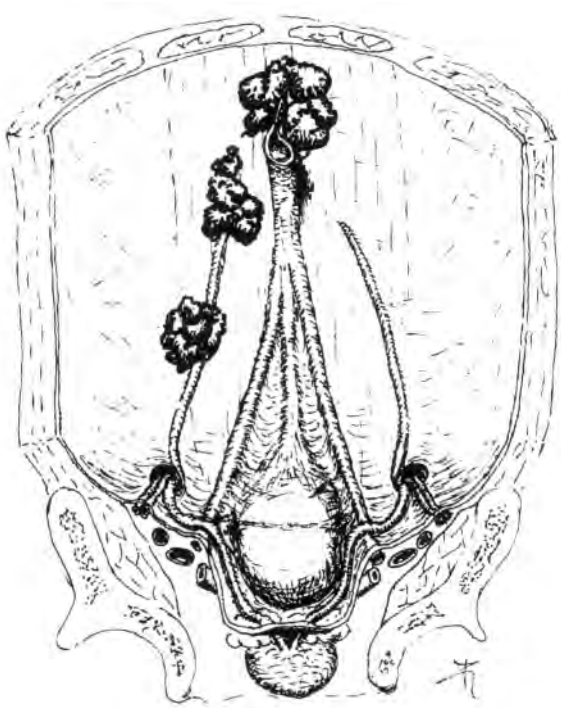


Fig.7.5 - The different pathways leading to a metastasis in the umbilicus.

The anterior abdominal wall, including the peri-umbilical region, has a rich arterial supply: the inferior epigastric and deep circumflex arteries, branches of the art.iliaca externa, and the superior epigastric artery, a branch of the art.thoracica interna.

As the umbilicus is a structure with a certain depth and is directly related to the extraperitoneal tissue it has a close relation with the anterior peritoneal surface. So neoplasms can extend through a peritoneal fold or propagate by contiguous extension.

In fact the umbilicus is a scar at the root of the umbilical cord. It is connected with several embryologic remnants:

- the vitteline duct (Meckel's diverticulum);
- the urachus or the allantois canal between the umbilicus and urinary bladder (ductus omphalomesentericus);
- the umbilical vein between umbilicus and the vena cava, which becomes the ligamentum falciforme and
- the umbilical arteries becoming the lateral vesico-umbilical ligaments at each side of the urachus.

Although suspected, propagation through embryologic remnants has only rarely beenproven.

Pathology

Umbilical metastases may appear under several forms (Coll et al.). The deposit can be dermal, subcutaneous or peritoneal and depend more or less on the pathway the cells of the primary have taken. A dermal deposit would appear to be associated with hematogenous spread, as with most of the cutaneous metastases. A subcutaneous nodule is common in breast cancer spread by subcutaneous lymphatic spread. This is also seen in laparoscopic scars resulting from gallbladder and other cancers.

Peritoneal deposits will extend from 'underneath' through this thinnest part of the abdomen and appear in the form of a bulging tumor within the umbilicus. If they can be distinguished on clinical grounds, the radiologic appearence of the three different forms will also be quite distinctive (Coll et al.).

Table 7.10 - Metastases to the Umbilicus
Literature Data, Review by Dubreuil et al. 1998

In MEN		In WOMEN	
Primary	Percent	Primary	Percent
Stomach	30%	Ovary	34%
Recto Colon (')	25%	Endometrium	12%
Pancreas	18%	Rect um Colon(')	12%
Bronchus	3%	Cervix Uteri	5%
Prostate	2%	Pancreas	8%
Other(")	5%	Gallbladder	3%
Unknown	17%	Breast	3%
		Stomach	9%
		Other(")	5%
		Unknown	9%

(') including small intestine
(") see text

Primaries

Reviewing the literature in 1998, Dubreuil et al. were able to collect 368 cases. For 71 patients, the gender was not stated in the reports.

The majority of the primaries involved are stomachal tumors in men and ovarian tumors in women. If both genders are taken together, however, stomachal cancers were the most frequent, 26.1% or one quarter (table 7.10).

Of all gynecological tumors, ovarian cancer accounts for the highest number, according to the hospital data from Lindeque et al. (table 7.11).

Table 7. 11 - Metastases to the Umbilicus
Incidence for Gynecologic Tumors
Data of Lindeque 1990

Ovarian cancer	8/274	2.92%
Endometrial cancer	4/203	1.97%
Cervical Cancer	15/1925	0.78%

Rectocolic and the few (6) small intestine tumors

accounted for 20.1% of all primarieswhen both genders are taken together. Pancreas accounted for 10% while in 11.2% the primary remained unknown, either after investigations, after autopsy or because autopsy was or could not be performed.
Ovarian tumors accounted for 64% of all gynecological tumors. In the group 'others', there were 5 bronchial cancers, 1 penis, 2 peritoneal mesothelio-mas, 1 urinary bladder, 1 kidney, 1 hepatocellular carcinoma and one myeloma.

SUBUNGUAL METASTASES

Patients with subungual metastases will usually report to the dermatologist. This is a rare condition and a commonly missed diagnosis, simulating a painful infection or paronichia.
Reviewing recently the literature, Cohen noted that in 92% it concerned the hand. In 44%, the lesion appeared before the primary was known, but this might be a publication bias. Radiologic evidence of bony involvement is observed in 92%. Bronchial cancers are the primary of 42% of the hand location and 35% at the foot, while genitourinary, mainly renal, are more frequent at the foot, 25% vs. 17%. Breast cancer account for about 10%.

METASTASES to the MUSCLES

Although muscles account for about half of the patient's volume, they are rarely involved even in cases of wide-spread metastases. Several hypotheses have been put forward to explain this low incidence. The continuous movement and the lactic acid environment are a possible explanation.

Table 7.12 - Metastases to the Muscles
Primaries and Site of Metastases
Review by Herrington et al. 1998

Primaries (52+15)		Site of muscle metast.	
Bronchus	26	Upper extr.+girdle	26%
GastroIntest.tract	13	Lower extr +girdle	40%
Kidney	10	Trunk	30%
Melanoma	2	Multiple sites	4%
Urinary bladder	2		
Unknown	2		
Others: skin, larynx, hypopharynx, tongue, cervix uteri, breast, prostate, ovary, pancreas, liver			

Incidence

Autopsy studies suggest that the frequency of muscle metastases is between 0.8 and 16%. It should be noted that not all muscles are examined, unless macroscopically evident. It is very probable that this metastatic site is underreported.

A literature review in 1998 found 61 patients reported (Herring et al.). They added 15 cases (table 7.12). The relative absence of breast and prostate cancer should be noted. In their own series, they had 7 patients in whom the malignancy was previously unknown, 3 of them from bronchial cancers (type 1 presentation). Similar data were recently reported by Pretorius et al.

Primaries

Several malignant tumors have been reported.
From 8 reports (totalling 61 cases), only 9 cases were supradiaphragmatic neoplasms.
It would seem that tumors of the kidney, the colon, uterus and rectum are the most frequent, but all have metastatic involvemement of either the iliopsoas or of the thigh. Could it be possible that retrograde spread occur?

Any tumor originating in or metastasizing in the retroperitoneum may invade the psoas muscle, due to its anatomical position, stretching from the diaphragm towards the pelvis.
The supradiaphragmatic tumors involves four bronchial cancers with either iliopsoas metastases (true metastases), two breast cancers, of which one with an iliopsoas metastases, one laryngeal cancer with a metastasis in the M.Soleus, one stomach cancer with a metastasis in the left trapezius and one esophageal cancer (no further details).

Pathways

Obviously an arterial route must be considered. Lodging of tumor cells within the muscular mass is the most probable.
They must be distinguished from the more common frank invasion through neighbouring tumors like most of the head and neck tumors invade the muscles of the floor of the mouth or the masticatory muscles. Another example is the invasion of the M.Pectoralis Major by a breast cancer.

Site

The anatomical site distribution parallels the distribution of soft tissue sarcoma. About half will be located in the lower extremity, but 26% in the upper extremity is more than the incidence of sarcomas (10%). Thirty percent of the muscle metastases are situated in the truncal musculature, including the chest wall, paraspinals, abdominal wall and iliopsoas muscle.

As far as the relative high frequency of involvement of the m.iliopsoas is concerned, detailed anatomical and pathological studies have revealed very illustrative data showing that it mainly concerns contiguous invasion either from adjacent bone metastases, or from a retroperitoneal lymphadenopathy (52%) (table 7.13) (Kenny et al.).

The M.Iliopsoas is an anatomical unit consisting of two parts, with a common tendinous insertion into

the trochanter minor. A potential pathway for spread lies between the two parts. This has been seen in 10 (28%). As the ventral rami of the upper four lumbar roots pass through the psoas, Since a rich lymphatic and vascular supply is present, irradiating pain and movement limitation is usual (fig.7.6).

Table 7.13 - Metastases to the Musc.Iliopsoas
Type of Invasion - Metastases (N=25)
Kenny et al. 1990

Adjacent Bony destruction		5 cases (20%)
Primary Ewing in iliac bone	2	
Lymphoma of L5	1	
Vertebral metastases	2	
Retroperitoneal Lymph.metastases		13 cases (52%)
Contiguous Nodal mass (adrenal, kidney)		3 cases
Local recurrence (kidney, colon)		2 cases
True intramuscular metastases		2 cases

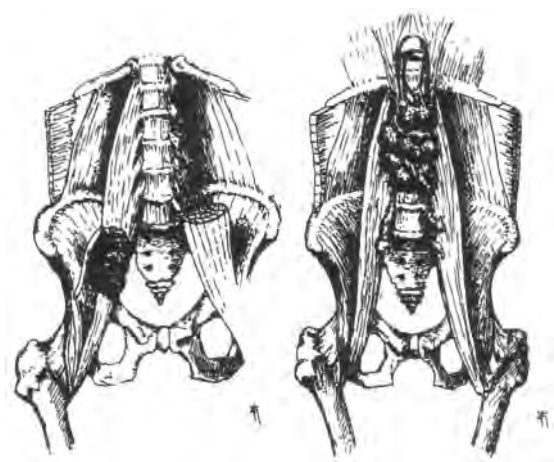


Fig.7.6 - Two possible sites of metastasis within or at the m.iliopsoas. Right, a pelvic node, left, a peri-aortic node.

In an earlier study, Lee et al. made a distinction between psoas involvement being by three mechanisms: total replacement due to true metastatic tumorous involvement and destruction, lateral displacement nearly always by metastatic lymph node masses and medial displacement by iliac tumors or metastases.

Reporting on 9 cases of muscular metastases, Folinais et al. mention 4 type 1 presentations. In 7 times, the M.Iliopsoas was involved, stressing the comparatively high frequency of involvement of this muscle. The primaries concerned were breast and bronchus as supradiaphragmatic tumors and kidney, colon, pancreas and cervix uteri tumors.

Pathology

Itwould appear that the tumor cells spread between the muscular cells without invading or destroying the individual myofibrils. This has been observed many times in cases with contiguous invasion.

Symptoms

Patients present either with a mass in the most superficial sites, and as shoulder, thorax wall and thigh, but many tell an intense pain, sometimes accompanied by a severe muscular contracture. This is relatively typical of the frequently involved m.iliopsoas.
Some cases have been reported where the metastasis presented before the primary was revealed (type 1-metastases).

Imaging

They were difficult or impossible to visualize in the pre-CT era. Present imaging methods have enabled detecting many more of these metastases, explaining some painful symptoms previously of unclear etiology.
The metastases are seen on CT as centrally located zones of decreased attenuation. The most reliable CTfeature for recognition of tumor involvement is the presence of irregular margins (Lenchik et al.). Larger bone destruction was a finding in the series reported by Kenny. Fascial plane disruption was not specific, as it occurs also in abcesses and hematomas.
In most of the lesions (25/30), Pretorius et al. observed at contrast-enhanced helical CT a rim-enhancing intramuscular mass with central hypo-attenuation.
The asymmetry in the size and/or density changes in the muscles are the clue to diagnosis, but must be differentiated from abcesses or hemorrhages. There is no specific, pathognomonic sign of malignity, but anamnesic features and a known treated malignancy should raise suspicion.

Differential Diagnosis

Considering age of the patients, sarcomas are about 30 times more frequent, so that histology is important.

VASCULAR TUMOR EMBOLI

The shedding of cells from a tumor is a common situation, as it is in fact the origin of all metastasis. If the cell groups have certain dimensions they can lodge in vessels larger than capillaries. Depending to the dimension of the embol, the involved organ can suffer an infarct eventually leading to complete organ failure with a definite clinical symptomatology. We have discussed this already in the chapter on lung metastases.
Peripheral tumor emboli are somewhat rarer, but they go probably unnoticed or undiagnosed. The symptomatology is mostly very acute, leading to catastrophical situations such as cerebrovascular incidents, mesenteric or cardiac infarcts and emboli within the lower extremities, and more rarely in the upper extremities.

Peripheral tumor emboli invariably have their origin in a primary or secundary lung tumor or the rare aortic sarcomas. Therfore, they are either secondary or third step metastases.
The anatomy of the circulation does not in fact allow peripheral tumor emboli, unless secondary lung metastases have already settled, from which new tumor cell-groups will dislodge and reach the aorta and the general circulation.
There are a few exceptions to this rule, for example a patent foramen ovale on one side (one case reported) or a direct invasion of the tumor, mostly sarcomas originating from or penetrating into the aorta or pulmonary veins.

Bronchial cancers are, as could be expected, the most fre-quent tumors leading to known peripheral tumor emboli. One unexpected finding is that sarcomas are the second most frequent cause (table 7.14).

A rare cause of peripheral arterial emboli is a sarcoma of the aortic intima. In virtually all cases it is the revealing manifestation of this uncommon neoplasm.

Table 7. 14 - Peripheral Tumor Emboli
Primary Tumors Involved (N= 69)(°)
Literature review by Chandler et al. and the author

Bronchus cancer	30 cases
Sarcoma (all types)	21
Thyroid cancer	3
Choriocarcinoma	3
Kidney	2

Larynx, Esophagus, Stomach, Adrenal, Testis, Renal Pelvis, Colon, Melanoma, Lymphoma 1 case each
(°) with cases of Duckworth, Nicholas, Kobayashi.

Symptomatology

Acute cerebral symptomatology or acute pain within the abdomen or any extremity are the main signs of a tumor embol. Ischemic symptoms or acute organ failure should raise the likelihood of an embol, particularly after pulmonary surgery. In some patients the embols will occur after pulmonary resection or manipu-lation. Spontaneous embolization is relatively rare.

Pathology

It has been described in almost all peripheral arteries. The aorta is the most frequently involved vessel, demonstrating the considerable size the embols must have in order to obliterate it. Cerebral and femoral arteries are also frequently involved. Embols of the visceral arteries will pose a challenge to diagnostic accuracy. There is no particular preferred site according to the type of primary. A literature review by Lipais et al. retrieved 39 cases, of which 19 from a bronchial primary. The arteries involved are in table 7.15. Four other cases concerned tumors of the arterial wall, but several more have also been described as will be discussed further.

At microscopy of non-acute cases, metastatic tumors may be seen to diffusely replace the endothelium with proliferation on the intima without invasion of the wall. Metastatic nodules can present in the parenchyma. Microscopic metastases can be found in other vessels too.

Table 7.15 - Peripheral Tumor Emboli
Arteries Involved
Review modified from Liapis et al. 1995

	Bronchial Tumor	
Artery Involved	Primary	Secondary
Common Femoral	5	6
Aorta Bifurcation	7	7
Internal Carotid	2	1
Coronary	--	2
Cerebral	2	4
Visceral	3	2
Iliac	1	2
Popliteal	1	1
Axillary - Brachial	2	1
Mitral valve annulus	--	1

Diagnosis

Every acute situation 'simulating' an embol or infarct in an oncology patient should raise the possibility of a vascular tumor emboli.
Several features should arouse suspicion (Greene et al.).

1. the presence of pulmonary metastases is in fact essential;
2. an infarction during or shortly after surgical manipulation on the lungs may be embolic;
3. multiple sites of arterial involvemement are not infrequent.

MUCIN TUMOR EMBOLI

As mentioned in respect of the lungs and the cerebral hemispheres, mucin emboli and venous thrombosis associated with mucin-producing cancers have been described in several central arteries including pulmonary, cerebral and coronary.
Cases from mucin producing carcinomas of the breast, the gallbladder, the stomach, the colon, the pancreas and the ovaries have been reported.
This is a very rare, to ther extent that it has been looked for and reported.Definite diagnosis of the case reported has always been obtained only at autopsy.
Nosanchuk et al. have reported that the mucin can be detected in peripheral blood smears.

METASTASES to the BONE MARROW and BONE

Although the skeleton receives only 10% of the cardiac output, metastases in the skeleton are very common compared to those with other tissues and organs receiving a far greater cardiac output (Jonsson et al.)
Of all the metastases, they are probably the best

known, the most studied and the most frequently encountered in oncology. It can also be said that they are also the most dreaded as they cause the most severe pain and complications.
We will first briefly discuss the mechanism of genesis of bone metastases, in fact initiating in the bone marrow.
Some specific sites will be given our attention: the vertebral column or spinal, metastases in the skull and skull base as the temporal bone; metastases in the extremities (long bones) and those in the hand and foot (acral).

Pathways

Bone metastases usually affect the axial skeleton. The pattern of distribution suggests that some physical properties of the circulation within the bone marrow such as the capillary structure and the sluggish blood flow are factors in the establishment of bone metastases. There is no doubt a correlation between the distribution of bone metastases and the distribution of active bone marrow, at least in adults.
Cancer cells spread to bone either by hematogenous dissemination or by contiguous extension from adjacent tumors or metastatic lymph nodes. There is another pathway, from the periosteal vessels for the cortical bone metastases, and this will be discussed now.
The medullary vasculature is formed by the ramification of the nutrient, epiphyseal and metaphyseal arteries feeding the sinusoids of the red marrow. As soon as the medullary artery enters the bone, it is abruptly divides into vessels with double layered walls, gradually branching to a single layered medullary sinusoids and cortical capillaries. The marrow sinusoids are lined with endothelial cells separated by amorphous gaps, allowing penetration by tumor cells (Berrettoni et al.).

The nutrient artery gives way to small branches to diaphyseal marrow sinusoids and continues to the metaphysis and/or epiphysis to end as dilated looped capillary vessels, then returning back and continuing into the meta-physeal system (fig.7.7). As the looped vessels and sinusoidal channels are much more dilated than intra-osseous arterioles, they allow for stagnation of blood flow and consequently, easier deposition of metastatic cells.

In those abover the age of 25 years, the distribution of bone metastases follows the distribution pattern of red marrow, with a high frequency of metastases in the spine, ribs, pelvis, skull and proximal femur and humerus. Most patients (but certainly not all) with metastases in the peripheral sites have advanced disease.

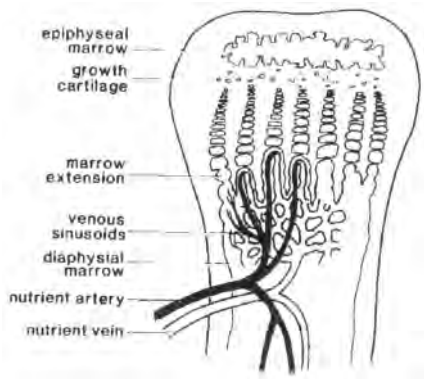


Fig.7.7 - The relation bewteen arteries, veins, venous sinusoids and red marrow. At the arterial-venous junction, a looped configuration is present (from Kricun, with permission)

As bone metastases have been observed in several regions without the presence of pulmonary metastases. Batson has, however, pointed out that there may be an anatomical explanation in the form of the so-called paravertebral plexus, which is connected with the azygos system. Under strain, the central venous circulation can modify its direction in order to organize an alternative pathway from the pelvi-abdominal organs towards the central part, the heart (Fig. 7.8).

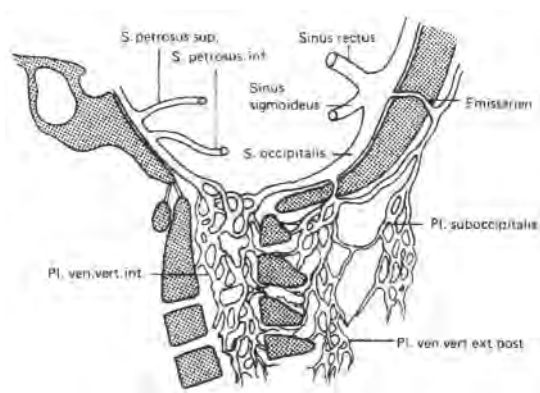


Fig.7.8 - Cranial part of the peri and intraspinal venous plexus, anastomosing with the intracerebral venous system (Gowin, with permission)

Anatomy

The spinal venous system can be divided into two internal epidural plexuses and two plexuses adjacent to the spine connected with the azygos-system (Gowin). The plexus venosus vertebralis internus consists of four interconnected valveless longitudinal veins, one pair anterior and one pair posterior. The anterior pair lies at the posterior wall of the vertebral body along the ligamentum longitudinale. At the cranial end they are connected with the basilar system (clivus), The posterior pair are within the spinal canal, at the inner site of the vertebral arcs. At the thoracal

and lumbar level, they are connected with intervertebral veins. The intervertebral veins come from both pre-vious plexuses and follow the spinal nerve outside the spinal canal at every segment. At the thoracal level, they join the intercostal vein and at the lumbar level the venae lumbales (fig.7.9).

The venae basivertebrales results from the joining of both vertebral plexuses, within the vertebral body towards the external plexus, the plexus venosus vertebralis externus anterior.
This external plexus consists of two parts, one anterior, along the vertebral spinal processes and one anterior at the ventral wall of the vertebral body. Both are connected with the azygos or the basilar system at the cranial end. The whole system can carry blood in both directions, depending on the hemodynamic situation of the main venous sytem.

Bone metastases in the sacrum and lumbar spine can adequately be explained by the flow in plexus of Batson. This is however more problematic for cervical spine and metastases in the shoulder girdle. This was addressed by Orhan et al. They state that there are numerous anastomoses between the pelvic veins and the systemic venous circulation, viz. hemorrhoidal, inferior epigastric, internal thoracic, hemiazygos and azygos veins (fig.7.10).

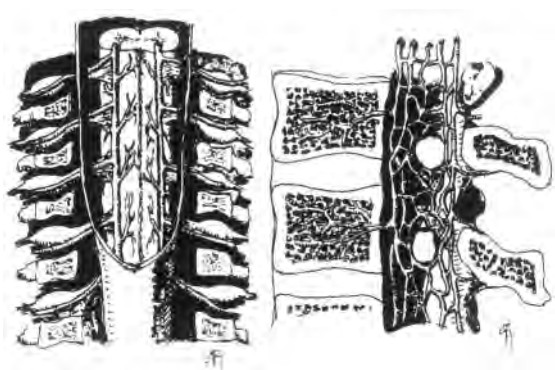


Fig.7.9 - Diagramatic drawing showing the intrarachidial and perivertebral venous plexus, in oncology called the Batson plexus or route, short-circuiting venous circulation of the abdomino-pelvic organs within the central thoracal and cervical regions

All these veins have the common feature that they all drain to the junction of the subclavian and jugular veins, where the vertebral veins also join via the azygos system. The neighbourhood of the ductus thoracicus make it to a crosspoint where several metastatic pathways join and become a site for spreading of tumor cells by backflow into the vertebral veins, viz. the cervical spine. The cephalic and subclavian veins can be the route for metastases in the clavicle and scapula.

Pathology

Bone metastases are found invariably in bones containing a high proportion of bone marrow.
More than 80% of the bone metastases originate from only five primary tumors: cancers of the breast, the prostate, the bronchi, the thyroid and the kidney. The other malignant tumors have a much lower propensity to generate bone metastases. This is discussed in the relevant chapters (part 2).
The spine, the pelvis and the ribs are involved in the first phase and are the earliest sites in most of the patients. The skull, femora, humeri, scapulae and sternum are involved later.
The different primaries do not differ much in their respective distribution of metastases. Prostate, cervical, bladder and rectal cancers have somewhat more pelvic metastases.
Solitary metastases are infrequent, except in renal cell cancers and neuroblastomas.
The apparent predilection of some tumors for some sites can be ascribed to anatomical relationships between venous drainage of the primary site and the blood supply to bones. Circulating cells may adhere preferentially to the endothelial surface only in specific bones.

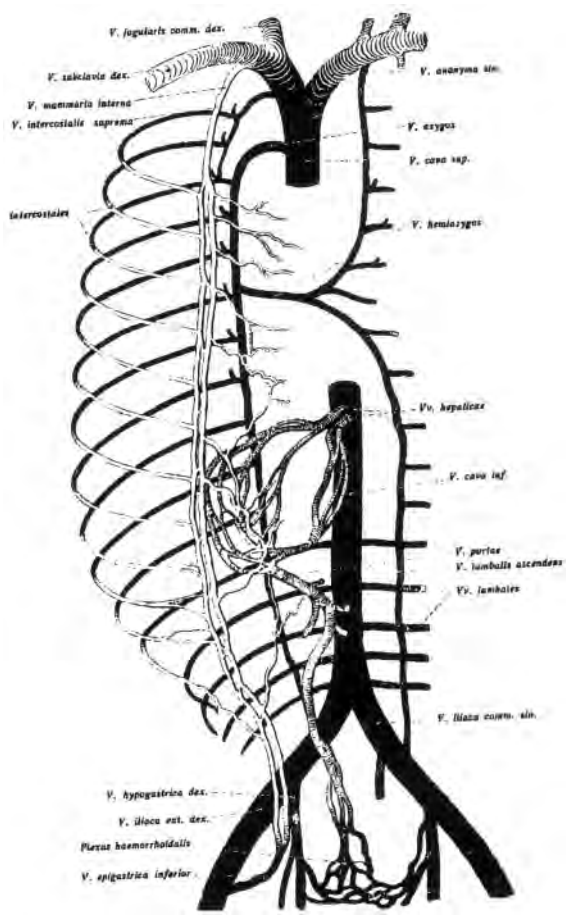


Fig. 7.10 - The azygos venous system connecting deep plexus with the central circulation.

The biochemical and cytological factors responsible for preferential growth in specific organs are incompletely understood.
The endothelial cells of marrow sinusoids lack a basement membrane, but have gaps between them that make the wall more penetrable by tumor cells than other elements. Another possibility is that one or more elements that specifically attract certain cells. A number of chemo-attractants have been described. Further discussion of this important aspect is, however, beyond the scope of the book.

It is well-known that bone metastases present in two classical forms: either osteolytic or osteoblastic (osteosclerotic) or both. The most frequent form, more than 80%, is the osteolytic form with local bone destruction and great propensity to produce fractures. The proportion of osteoblastic metastases is largest for prostate carcinoma. An overview of the radiographic appearance of skeletal metastases is shown in table 7.16.

Some particular radiological forms have been described.
Several authors have pointed to the fact that even at autopsy, microscopic foci can be found in bones, especially vertebrae, without macroscopically visible metastases. Grunow et al. found at autopsy only microscopic bone metastases in 17.4% of 334 oncology patients.

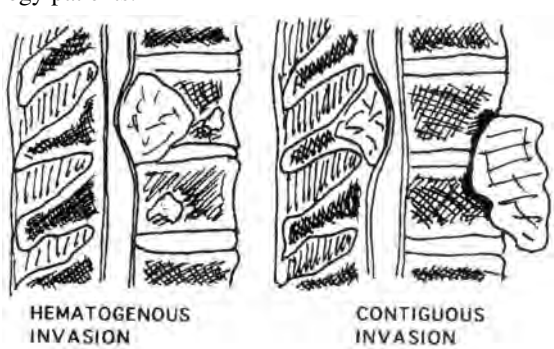


Fig.7.11 - Metastases to the vertebral body can be either hematogenous (left) or an invasion from a contiguous mass, usually a metastatic lymph node (right)

Table 7.16 - Bone Metastases
Radiological Appearance for the most common Tumors
Modified from Wilner

Lytic, sometimes mixed or occasionally blastic
Breast, bronchus, stomach, pancreas, rectum,
Colon, uterine cervix, prostate, urinary bladder
Invariably lytic
Kidney, thyroid, head and neck, adrenal,
Endometrium, skin cancer, melanoma
Lytic or mixed
Esophagus, liver, galbladder
Blastic : Prostate
Blastic frequently mixed:
Carcinoid (abdominal or bronchial)

Symptoms - Presentation

While pain is an important sign or first symptom, not all skeletal metastases have pain as first sign reported by the patient. An important data set has been reported by Conroy et al. in two reports on 429 patients, later updated in some aspects on 578 patients (table 7.17). The authors state also that the proportion of asymptomatic patients has risen progressively from 15 to 25% in recent years. This can be explained by the progressive increase of patients diagnosed at earlier stages in their disease.

Table 7.17 - Bone Metastases
Presentation - First Signs (N=578)
Data of Conroy et al. (1993)

Bone pain	78.7%
Neurological Symptoms(')	12.7
Pathological Fracture	8.0
Tumor forming	3.3
Hypercalcemia	2.9
General condition - Anemia	0.5
No Symptoms:	
Found during staging	8.0
At follow-up	3.7

(') epidural compression and other

Furthermore, they found that in 23% of the patients, bone metastases were the first sign of an unknown primary, which remain undetected in about half of the cases (see further).

Site of Metastases

Of all patients with bone metastases, 47% had no other metastatic site. At death, 74% will only have bone metastases.
In another 47%, other metastases preceded (16%) or were found simultaneously (31%) at first diagnosis (Conroy et al.). The other metastatic sites were pulmonary in 41%, hepatic in 29%, pleural in 20%, nodal in 17%, cerebral in 16% and cutaneous in 14%, either only or in a mixed pattern.

Table 7.18 - Bone Metastases
Sites of the metastases (N=578)
Series of Conroy et al. 1993

Skull		25.7%
Vertebral Column	Cervical	23.4%
	Thoracal	53.8%
	Lumbar	52.1%
	Sacrum	17.0%
Shoulder girdle		15.9%
Ribs		46.5%
Pelvis		45.6%
Upperlimbs	Humerus	15.6%
Lower limbs	Femur	35.0%

Such global data invariably depend on the respective number of the different primaries. The series by Conroy et al. seems to us the best documented. It contained 33% breast cancers, 22% bronchial cancers

and only 8% prostate cancers.
As already mentioned bone metastases are more frequent in the axial skeleton (table 7.18).

Diagnosis (of Skeletal metastases in general)

Radiology and isotope-scintigraphy have both an important 'first-line' diagnostic impact. Both have a false negative rate of 3.9% and scintigraphy a false positive rate of 5.8%.
An interesting point is the fact that in patients subjected to both the radiological survey and a total body scintigraphy, the latter adds 70% supplementary foci to the first (Conroy et al.).
A correlation was sought between pain and positivity of scintigraphy in breast and prostate cancer by Palmer et al. (table 7.19).

Pain may well be aspecific and can be caused by several bone disorders, so that not every pain is of metastatic nature. Scintigraphy can also be positive in patients without pain, as is common knowledge.

We will discuss imaging methods further in the chapter on spinal metastases.

Table 7.19 - Bone Metastases
Correlation Pain and Scintigraphy
Data of Palmer et al.

	Scintigraphy		
Breast cancer (N=131)	Meta	No meta	Dubious
Pain present (N=72)	57%	36%	7%
No pain (N=59)	19%	76%	5%
Prostate cancer (N=64)			
Pain present (N=38)	82%	13%	5%
No pain(N=26)	34%	42%	23%

Pain present
Breast cancer: in 79% of patients with metastases
Prostate cancer: in 78% of patients with metastases

OSTEOBLASTIC METASTASES

The large majority of bone metastases are osteolytic, meaning a preponderance of the osteoblastic over the osteoclastic activity. The incidence of osteoblastic metastases differs according to the primary tumor. The repartition over the whole skeleton is also different. As well-known, prostatic cancer has the highest incidence (table 7.20) Exceptional cases have been reported in other cancers.
Osteoblastic metastases are almost all located in the axial skeleton, including the proximal humerus and femur. Distal and acral bones are very rarely involved.
A particular aspect is the ivory vertebra as the most evolved osteoblastic disease: very frequent in prostatic cancer of course, but also in lymphomas and plasmocytomas. When the primary is not immediately discovered, the ppossibility of metastatic carcinoids should be considered (chapter 14). They must be differentiated at imaging (radiology) from a number of benign osteocondensing lesions, such as osteopoikilia, myelofibrosis, fluorosis and many other conditions (see review by Buthiau et al.).

Table 7.20 - Osteoblastic Bone Metastases
Incidence
Review by Buthiau et al.

Primary	Incidence
Prostate	55-85%
Breast	10% -25% mixed
Bronchus	5% (princ.small cell-adenocarcinoma)
Carcinoid	majority
Nasopharynx	UCNT (*): 25%
Urinary Bladder	rare, except when prostate involved
Ovary	very rare
Renal cell	very rare
Testis	very rare
Endometrium	very rare

(*) UCNT: undifferentiated cancer of nasopharynx

CORTICAL METASTASES

Metastases in the long bones are, as has already been pointed out mostly located in the medullary zone. Recently, a relatively rare subset of cortically based metastases, predominantly in the long bones was isolated and addressed by the literature. Previously only case reports appeared, but later a number of institutional series have been reported.

Table 7.21 - Cortical Bone Metastases
Patterns according to Greenspan et al.

Pattern	Description
I	Small focal lesion, marginal cortical destruction
II	Large osteolytic cortical destruction
III	Saucerized intracortical destruction with well-defined periosteal reaction
IV	Predominantly cortical destruction extending into soft tissue as well as into the medullary cavity

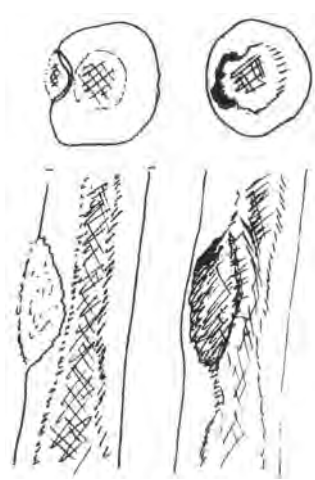


Fig.7.12 - Comparative aspect between a cortical (left) and a medullary (right) metastasis in the bone

Four patterns have been distinguished by Greenspan et al. (table 7.21). They can be viewed as progressive grades of the metastases. Needless to say, that the fracture risk also increases with thise patterns, as progressively more cortical bone is destroyed (fig.7.12).

Incidence

Cortical bone lesions accounted for 25% of the patients or 22% of the metastatic lesions in the appendicular skeleton. This means that they are, in fact, not rare, but not recognized as such.Particularly, more than one third of these are from bronchial cancers, apparently almost all adenocarcinomas (Miric et al.).
We have grouped the three reported seriesaccording to the primaries and the metastatic sites (table 7.22). The absence of prostate cancers in this group is striking.
The femur is the main site for cortical metastases; more than three quarters of all the lesions. The lower limb accounts for 87% of all lesions.
Quite a number are solitary metastases (no other metastatic site), single 20/27 (Hendrix et al), and a few were the first presentation (7/18) (Miric et al.).

Table 7.22 - Cortical Bone Metastases
Primaries and Site Involved
Data from 3 published series (')

Primary		Site of Metastasis	
Bronchial cancer	25 (35.2%)	Humerus	7
Kidney	18 (25.3%)	Radius	1
Breast	12 (16.9%)	Ulna	2
Gastrointestinal	2	Femur	56 (73.6%)
Various	8	Tibia	10
Unknown	6	Fibula	0

(') series by Coerkamp et al. (N=26); Hendrix (N=27) and Miric (N=18)

Greenspan et al. reported on 11 patients, all bronchogenie cancers, from 100 consecutive patients with skeletal metastases. The 11 patients had a total amount of 22 lesions, all located in the femur, mainly in the upper half. Deutsch et al. had previously reported on 6 cases, also all from bronchogenic cancers: one in the skull, one at the hip, one at the tibia and 3 in the femur.

Pathways Pathogenesis

Previously, the blood supply to the cortex was thought to come from the medullary cavity. More recent studies have shown that the cortex has a distinct intracortical vascular network of intercommunicating capillaries, supplied by anastomotic branches from periosteal, medullary and nutrient artery vessels.
Arterially disseminated cells could therefore arise in an intra-cortical or subperiosteal location via nutrient branches, without involving the medullary vascular circulation of the bone (fig.7.13).
When the area of bone cortex is considered, 26/35 of the tibial and femoral lesions occurred in the posterior or medial quadrants, probably correlating with the local cortical blood supply.

PERIOSTEAL SUNBURST REACTION

Spiculated or 'sunburst' reaction is a rare periosteal finding in metastatic disease. It will erroneously suggest a primary sarcoma. It was first described by Brunsweig in 1936. Several case reports exist, but according to Bloom et al, they are not well codified, so that not all can be considered as such. They found 50 cases in the literature and added 20 of their own.

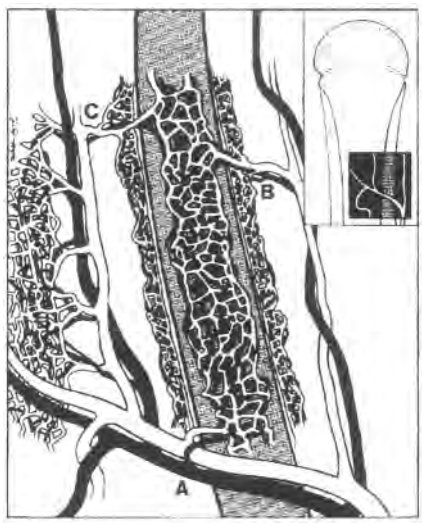


Fig.7.13 - Cortical circulation of a long bone. The capillary system of the cortex from medullary (C), periosteal (B) and nutrient (A) arteries. Any of the three vessels can transport cells to become an intracortical metastasis without involvement of medullary cavity (from Hendrix et al., with permission)

Pathology

Four types of periosteal have been distinguished by Norman et al.
1. a lamellated reaction (onion peel);
2. a perpendicular or spiculated (sunburst) appearance;
3. a dense periosteal reaction which is difficult to differentiate from thickened cortical bone and often associated with osteoblastic metastases;
4. the Codman or reactive triangle at the margin of the lesion.

The sunburst periosteal reaction is mainly associated with osteoblastic metastases.The spicules of the sunburst are variable in appearance, being either perpendicular to the cortex or slightly angulated. They may be short or long, fine or coarse, few in number, or forming a well-developed palissade (Bloom et al.).
Several present with a well-defined either palpable or radiologically visible soft tissue mass.

The presence of periosteal new bone in the spiculated fashion is difficult to explain. One possible explanation should be that as the tumor grows, the

periosteum is detached from the bone, leaving a loose attachment (by thin fibers) of periosteum to the cortex. New bone is then laid along the direction of the vessels, resulting in the spiculated appearance (Vilar et al.).

Primaries

Contrary to the cortical metastases, prostate cancers are the major primary concerned (29%) (table 7.23 - 24). They are much more frequent in the appendicular skeleton than the classic metastases.

Table 7.23 - Bone Metastases with Sunburst Periosteal Reaction
Primary Tumors Involved (N=70)
Literature review by Bloom et al. 1987

Prostate	29%	Urinary Bladder	4%
Bronchus	10	Breast	4
Neuroblastoma	10	Thyroid	3
Colon - rectum	7	Testis	1.5
Retinoblastoma	6	Kidney	1.5
Carcinoid	6	Esophagus	1.5
Stomach	4	Hodgkin	1.5
Adenocarcinoma NOS	11		

Diagnosis

As the periosteal sunburst reaction is common in sarcoma, differential diagnosis is necessary and important for treatment. The age of the patients with metastases is, however, much higher than for osteosarcomas.

Table 7. 24 - Bone Metastases with Sunburst Periosteal Reaction
Bone sites Involved (N=70)
Literature review by Bloom et al. 1987

Skull - mandible	15%	Lumbar Spine	2%
Chest cage	13	Pelvis	15
Humerus	14	Femur	22
Forearm- hand	4	Tibia - fibula	15

HYPERTROPHIC METASTASES (VISIBLE)

Skeletal metastases are normally hidden below the surface of the body. A rare form exists which can be palpated and even seen due to its exuberant or hypertrophic growth. They can lead the patient to a consultation due to pain if present, mechanical hinder or for esthetic reasons. Two types have been distinguished, one with a regular architecture and one irregular, probably labeled as a pseudosarco-matous type (Bétoulières et al.). At radiology, they present like (chondro)-sarcomas, usuallly with a multilocular osteolysis but with dense zones. Pathological fractures have been described. While clinics and radiology will usually suffice for diagnosis, it can be confirmed by fine needle aspiration cytology or even biopsy.

This expansive form of skeletal metastases is hardly discussed in the literature and mainly only in the French literature (les métastases hypertrophiantes, pseudosarcomateuses ou pseudo-aneurysmales).
When the concerned bone is near the skin, a frankly expanding and visible tumor can occur. This type of metastases has to be treated like other types, but the clinical appearance can be misleading due to its rarity and confounded with a soft tissue tumor.
They can reach a relatively large volume and curiously enough, do not regularly lead to pathological fractures. Quite a number are solitary metastases.
The visible type can, of course, only be seen in the limbs or superficial bones of the thoracic skeleton, but also in the cranial vault, where they can be palpated.

In our iconographical archive, spanning 40 years of private practice, we found nine patients, here grouped on table 7.25. Clinically, the metastases present as a visible and prominent firm swelling, rarely pulsating as at the sternum. At auscultation, a souffle can sometimes be heard, hence their name: pseudo-aneurysmal metastases.

Table 7. 25- Hypertrophic Bone Metastases
Personal series

Pat.	Site of M	Primary cancer
F65yr	sternum	papillary thyroid carcinoma
F45yr	sternum	follicular thyroid carcinoma
M66yr	ankle	epidermoid bronchial carcinoma
F68yr	foot	ductular adenocarcinoma breast
F61yr	humerus	renal cell carcinoma
M66yr	mandible	adenocarcinoma colon ascendens
M59yr	rib	renal cell carcinoma
M88yr	clavicle	prostatic adenocarcinoma
M70yr	humerus-scapula	adenocarcinoma of Vater

Reviewing the literature in 1992, Sanzari et al.were able to retrieve 18 cases, adding two from their files (table 7.26). In their review, only tumors of the GIT are involved.

Table 7.26 - Hypertrophic Bone Metastases
Literature Review (Sanzari et al.)

Primaries		Site of Metastasis	
Esophagus	2	Humerus	4
Liver	2	Femur	8
Colon	5	Iliac bone	5
Cecum	1	Scapula	2
Intestine	1	Tibia	1
Sigmoid	5		
Rectum	4		

According to Reboul, they have a similar radiological appearance to Paget's disease. Of 150 patients studied with metastases, 14 presented with the 'hypertrophic' type. In a review on the pathology and radiological aspects of skeletal metastases, Dargent et al. mentioned a 6 to 10% incidence of hypertrophic metastases. In the reported iconography, there is a case is presented with a metastasis in the tibia from a uterine cervical carcinoma. Franck et al. and Roblot both

described one case each in the pelvic bones of patients with prostatic carcinoma.

Metastases within the sternum (see further) are not rare but particularly not well discussed in the literature. Two hypertrophic metastases from thyroid cancer in the sternum were reported after resection by Ozaki et al. Of the 4 thyroid cancers, 2 had sternal metastases. A number of cases of hypertrophic metastases from kidney and prostatic cancer have been reported. A particular and rare form of this is the pulsating form. The abundant vascularity of the metastases predisposed them to an arterio-venous shunt, resulting in a pulsating tumor. Many cases have been reported concerning renal tumors and a few from thyroid cancer (Estrera et al.).

A pulsatile swelling at the sacro-iliacal region was the presentation of an aged women with a thyroid cancer (Kuntz et al.). They state that in fewer than 1% of cases involving bone metastases, the pseudo-aneurysmal type of metastasis should occur . Citing a report by Bobin et al. and a thesis by Cerbay, they report that of 100 cases of hypertrophic bone metastases, 60% probably originate from thyroid cancer, 35% from kidney cancers and rarely any from hepatocellular carcinoma. Renal and prostatic carcinoma are also cited as primaries.
About 18% of the bone metastases from thyroid carcinoma are of this type. Of all hypertrophic metastases 40% should occur in the sternum, 20% in the skull and 10% in the pelvis. A case presenting in the medial end of the clavicle as first sign was reported by Bose et al.

Of 12 cases of thyroid metastases in the skull and three other ones, all but one were of the expansive type, as we have been able to deduce from the reported images. The fact that of these only 1 occurred in man, confirms the well-known higher incidence of skeletal metastases from thyroid cancer in women (Chapter 13).
Recently, one case of forehead mass was reported in a 33yrs young female which turned out to be a cystic skull metastases from an unknown primary, afterwards demonstrated to be a renal cell carcinoma.

METASTATIC ARTHRITIS

Arthritis resulting from metastatic involvement within juxta-articular bone or synovial tissue is poorly recognized and hardly discussed in the literature. Normally the joints are considered as never being involved, as the cartilage is supposed to be a barrier against further destruction. Nevertheless, a number of cases have been described, presenting as arthritris, misleading the clinician, the radiologist and even the oncologist. Some were even type 1 metastasis (table 7.27).
Arthritis as a metastatic disease can result from two causes; a direct metastatic invasion of the synovium without any adjacent bone involvement, or by infiltration of the synovium from adjacent bone metastases similar to reactive synovitis.

It is strange that the reported cases are almost all monoarticular, some with effusion. The knee is the most frequently concerned, followed by the hip and of hand and foot joints. At radiology, there is a progressive decalcification, although initially only faint or no abnormality is noticed. In a few cases, positive cytology of the synovial fluid was obtained, but this is not necessary criterion as it always concerns an invasion from the juxta-articular bone.
In the period up to 1980, 11 cases had been reported. Bronchial carcinoma is the main primary, followed by breast. Colon, bladder and prostate were the others (Murray et al.). Since then, cases from renal cell cancer at the shoulder (Fremland) and three more cases from a bronchial cancer, with one at the sterno-clavicular joint (Fam et al.; Murray et al.) and of breast cancer (Menon et al.) have been documented.

Table 7.27 - Metastatic Arthritis
Literature Review

Affected Joints N=43 (Brooks)		Involved Primaries N=43 (Schwartz)	
Knee	23 (53%)	Bronchus	16 (5F)
Hip	5	Kidney	7 (1F)
Shoulder	5	Melanoma	3 (1F)
Sternoclavicular	3	Colon	2 (1F)
Elbow	2	Breast	4 (4F)
Wrist	2	Uterus	2
Interphalang.	3	Unknown	5 (1F)
Ankle	3	Other	6 (2F)°

(°) male : bladder, prostate, tongue, pancreas; female: stomach, sarcoma

Of the 16 patients with bronchus cancer, the knee was involved in 9.
Reviewing the literature, Munn et al. retrieved 27 previously described patients with joint effusions and a solid tumor. Cytology was diagnostic in 50%, and synovial biopsy in 11/16, or 69%. In seven 'negative' cases, the diagnosis was made at autopsy.
Metastatic arthritis must be differentiated from 'rheumatoid' arthritis, a frequent paraneoplastic manifestation. The diagnosis of rheumatoid arthritis is nevertheless not infrequently made, especially in acral metastases, as this condition is much more common.

METASTASES to the SKULL

Metastases to the skull occur in 15 to 25% of patients. The metastases in the cranial vault are less symptomatic than those of the cranial base, because of the compression/involvement of the different cranial nerves.

Metastases to the Cranial Vault

In cases of widespread bone metastases as happens in

breast and prostate cancers, this site is a common one. It also has been reported in all other cancers, but more as an incidental finding.
Except for true 'bony' metastasis, the cranial vault may be invaded, with extensive destruction, from skin primaries or secondaries, or from dural metastasis, as has been reported for bronchial and prostate cancers. Constans et al. have reported on a number of large metastases, mainly of the contiguous type, from scalp metastases.

Metastases to the Skull Base

This is also a commonly occurring metastasis originating from osteophylic tumors.

Clinically, four groups can be distinguished. The orbital syndrome (discussed in the chapter on H&N-metastases), the parasellar syndrome (discussed in the chapter on CNS-metastases), the middle fossa syndrome, the jugular foramen syndrome and the occipital condyle syndrome.
The middle fossa or gasserian ganglion syndrome is caused by lesions of the skull base at the middle fossa. The trigeminal nerve is involved to a greater or lesser extent, resulting in numbness of the face, paresthesias or pain in the second and third region of the trigeminal nerve. In the series by Greenberg et al, half of the cases were from breast cancer, the others being prostate, bronchial and other primaries.
The jugular foramen syndrome presents with hoarseness and/or dysphagia. It involves the cranial nerves IX to XI, rarely XII. Glossopharyngeal neuralgia is sometimes present, such as pain behind the ear at the involved site. Differential diagnosis with the paraganglioma can be necessary when the patient has no known cancers. Head and neck cancers are a common cause, mostly nasopharyngeal tumors.
Metastases in the occipital condyli are discussed later.

CT and MRI are the appropriate imaging methods and both represent an enormous asset in the diagnosis, compared with some decades earlier. On T1W images, the hallmark of metastatic disease is the replacement of normal bone marrow with tissue of decreased signal intensity, while on T2W the metastases are generally hyperintense relative to adjacent bone. Nevertheless, it cannot differentiate a secondary involvement from a primary tumor (Ginsberg).

Metastases to the Temporal Bone

Metastases to the temporal bone have received some attention in the literature, in view of the difficulties in diagnosis, due to the complex neurological symptomatology, easily confounded with other pathologies of the internal ear and skull base.
Metastatic cells can reach the temporal bone through arterial spread within the bone marrow or by dissemination within the subarachnoidal space from cells in the cerebrospinal fluid, or from leptomeningeal metastases, into the internal auditory canal (Hill et al.).

The area of the bone that still contains bone marrow will be invaded first. The petrous apex bone marrow is the most frequently involved part, while the mastoid cells are less frequently invaded. Reviewing the literature on 141 reported cases, Streitmann et al. were able to provide data illustrating the distribution of metastatic foci within the bone (table 7.28). In almost all cases of involvement of the internal auditory canal, cytology of the CSF will be positive, confirming the resultant spread. The primaries involved are in table 7.29.

Table 7. 28 - Metastases to the Temporal Bone
Site distribution (N=141)
Literature Review by Streitmann et al.

Pars Petrosa	46 (32.6%)
Internal Auditory Canal	22
Mastoid	12
External auditory Canal	11
Middele Ear	5
Pars squamosa	1
Multiple sites	29
Unspecified	15

Table 7.28 - Metastases to the Temporal Bone
Primary Tumors (N=141)
Literature Review by Streitmann et al.

Breast cancer	35 (24.8%)	Urinary Bladder	3
Bronchus	24 (17.0%)	Melanoma	5
Kidney	13	Colon	3
Stomach	9	Lymphoma	2
Prostate	8	Unknown primary	16
Thyroid	6	One of the following:	
Larynx	5	ovary, Ewing, tonsil, rhabdo-	
Uterus	4	myosarcoma, seminoma testis,	
		nasopharynx, rectum, pancreas	

Subarachnoidal spread involves the pia-arachnoid membranes, and has a curious predilection for invading the internal auditory canal, often bilaterally. Tumor cells that have invaded the scala tympani may infiltrate the bony wall of Rosenthal's canal or the osseous spiral lamina (Imamura et al.). Persistent tinnitus and rapidly progressing sensineural hearing loss are the usual beginning manifestations.
Based on the studies of Berlinger et al. different patterns of involvement can be discerned (table 7.30).

Primaries

In the already mentioned literature review by Streitmann et al., 24.8% originated from a breast cancer and the others from a series of 21 different tumors. It would appears that this bone is one frequently called at by many different primaries (table 7.31).

Table 7.30 - Metastases to the Temporal Bone
Clinical Patterns observed
Modified from Berlinger et al.

1. Isolated metastases within any part of the bone
2. Meningeal carcinomatosis with invasion of the auditory canal and subsequent infiltration of cranial nerves VII -VIII
3. Meningeal involvement by a primary intracranial tumor extending to the temporal bone
4. Leukemic, lymphomatous or perineural infiltration of the petrous apex.

A well-documented series was recently reported by Gloria-Cruz et al., based on an autopsy study of 212 patients of whom 47 or 22% had metastases to the temporal bone. The involvement was bilateral in 62% of these patients. Most metastases were clearly hemato-genous (77%) and the apex petrosi was the dominant site involved (83%).
The authors stress that in no case was it the sole site of metastasis. In one case, the primary (prostate cancer) was unknown before autopsy. They made a detailed study of the site involved within the os temporale (table 7.32).
Three years after surgery for breast cancer, a F76 presented with a pulsatile tinnitus, audible over the right mastoid region. A blue colored mass was seen pulsating behind the tympanic membrane. Destruction of the temporal bone extending to neighbouring bones of the skull base saw revealed at CT (Vasama et al.).

Table 7.31 - Metastases to the Temporal Bone
Primary Tumors - Autopsy study (N=47)
Data of Gloria-Cruz et al.

SupraDiaphragmatic		Infradiaphragmatic	
Breast	10(21.3%)	Prostate	5 (10.6%)
Bronchus	6 (12.8%)	Cervix Uteri	3 (6.4%)
Brain	2	Liver	3
Tonsil	1	Stomach	2
Soft palate	1	Colon	1
Thyroid	1	Duodenum	1
Larynx	1	Bladder	1
Oral Cavity	1	Ovary	1
Other	Melanoma	4	
	Bone	1	
	Muscle	1	
	Unknown	1	

Table 7.32 - Metastases to the Temporal Bone
Site involved within (Autopsy study N=47)
Data of Gloria-Cruz et al.

External Ear	9.2%	Osseous Labyrinth	
Middle Ear	21.1	Otic capsule	13.2%
Eustachian tube	14.5	Vestibule	9.2
Mastoid	27.6	Cochlea	10.5
Petrous apex	82.9	Membranous labyrinth	
Internal canal	27.6	Semicirc. canal	3.9
Facial nerve	19.7	Saccule	3.9
		Utricle	3.9
		Cochlear duct	3.9

Symptomatology

The patients present with a variety of otologic symptoms such as hearing loss, facialis paralysis, otalgia, aural discharge, tinnitus and others. In more than 75% facialis paralysis will be the first symptom.
Detailed descriptions of the symptomatology were recently provided in two series (table 7.33). The symptomatology exhibits the usual differences. It is understandable however that in a surgical series, all patients are to be expected symptomatic, while in an autopsy series about one third would be asymptomatic.

Table 7.33 - Metastases in the Temporal Bone
Symptomatology

Symptom	Zhang 1999 N=33 (‘)	GloriaCruz 2000 N=47(“)
Otorrhea	78.8%	4.2%
Otalgia	45.5	8.5
Facial palsy	36.4	14.9
Hearing loss	30.3	40.4
EAC mass	24.2	4.2
Periauricular	9.1	--
Vertigo	3.0	14.9
Tinnitus	3.0	12.8
Nystagmus	--	4.2
No Symptoms	--	36.2

EAC: external auditory canal
(‘) surgical series
(“) autopsy series

Metastases to the Occipital Condyli

This is a rare metastatic site, but not easily missed because of the relatively specific symptomatology.
Occipital pain, complicated by palsy of the hypoglossus or other cranial nerves, is the hallmark of this site, though it must of course be differentiated from meningeal and pontine lesions. CT is the clue to diagnosis, but it needs images in the ‘bone-window’.
A series of 9 cases has been reported by Loevner et al. In five of these patients, it was the first sign of an unknown tumor, stressing the importance of the clinical and radiological diagnosis.

Metastases to the Mandible

The mandible is not an unusual place for metastatic involvement, which will mainly be from malignancies with predilection to metastasize to bone. Single metastases occur, but they are usually associated with widespread osseous metastatic disease.
Distant primaries will obviously reach the mandible by hematogenous spread. They must be differentiated from invasion by tumors of the gingiva and of the floor of the mouth, and from ingrowing metastatic submandibular lymph nodes (see further).
As mandibular metastases are part of a diffuse disease, they are almost never examined at autopsy, so that incidence data are lacking. They are probably as frequent as diffuse metastases, at least in the most

frequent primaries. Nevertheless, there are some particularities in the type of primaries involved. Hirschberg et al. retrieved 390 published cases from the english literature up to 1991. While bronchial cancer is the most frequent primary in men (22.2%), breast cancer is it in women (42%) (table 7.34).

Neuroblastomas, retinoblastomas and medulloblastomas are frequent primaries. An unexpected finding in this review is the low number of liver cancers, as they are well-represented in the world literature of the last decade. Twenty-five percent of them represent first sign of hepatocellular carcinoma. Tthe high number of thyroid cancer in female patients, with several first sign presentations, should be noted.

Table 7.34 - Metastases to the Mandible
Primary according to gender
Literature Review by Hirschberg et al. 1993

Men (N=184)(°)		Women (N=200) (°)	
Bronchus	41 (22.2%)	Breast	84 (42%)
Prostate	22	Neuroblastoma	17
Kidney	19	RectoColon	16
Neuroblastoma	17	Female Genital.	15
Bone tumors (')	17	Bone tumors (')	12
Liver	13	Kidney	12
Testis	10	Thyroid	12
Rectum Colon	8	Retinoblastoma	9

(°) only primaries with more than 7 cases are listed
(') bone sarcomas, myeloma.

We also noted in the literature cases from tuba, trophoblastic and many other carcinomas.
A literature review by Aniceto et al. found that a mandibular metastasis was the first symptom in 25 to 30% of all cases reported. Such spectacular diagnoses are certainly much more prone to be the subject of a publication.

Pathology

The large majority of the tumors metastasizing to the mandible are undifferentiated carcinomas or adenocarcinomas. There are almost no epidermoid cancers, pointing to a 'soil and seed' factor.
A relationship between the site of metastasis within the mandible with active bone marrow has been postulated. On the other hand, we think that the vascularity of the mandible may play a role. Another hypothesis is that there might be the 'reactivation' of bone marrow activity due to the widespread involvement of bone marrow in the spine and elsewhere, so that the bone marrow of the man-dible again becomes active as compensation.
The vascularisation and the active red marrow can explain the most common location of metastase, in the molar and premolar region. Multiple sites within the mandible are uncommon.

One unusual site of metastasis is the condyle of the mandible. This site is rarely involved. A literature search by Johal et al. claimed to have retrieved only 21 cases, mainly from breast and bronchial cancers. Further data are not at hand. A type 1 or revealing metastasis in the mandibular condyle of an epidermoid carcinoma of the bronchus has been reported by Peacock et al. Its rarity may be due to the low amount of bone marrow at that site. In about half of the cases, the presentation is like a TMJ syndrome, with pain and trisms, mandibular deviation eventually associated with a swelling and radiologic evidence of osteolysis or pathologic fracture.

The mandible was examined in 62 cancer patients coming to autopsy, by Hashimoto et al. The mandible were grossly normal in all and at specimen radiology no pathology was disclosed. Nevertheless at microscopy, involvement was noted in 10 or 16% of the cases. There were 3 stomach cancer patients, 2 lungs, 2 urinary bladder and one of breast, prostate and pancreas cancer. In all, extensive involvement of the posterior part including the condyli and coronoid process was observed. This study stresses the fact that the mandibular metastases will go unnoticed in many patients.

While several case reports mention a recent tooth extraction, only Hirschberg et al. reviewed the pertinent cases. They found 55 cases with adequate data and description. The mandible was affected in 78% of the cases. As in the other cases, the most frequent primaries were bronchial cancer in men and breast cancer in women. While there is no doubt that the tooth extraction was done for good reasons, a mean time of 2 months between extraction and diagnosis points to the fact that the metastasis was already present at that time. The most frequent site was the second molar.

Symptoms

The most frequent symptoms are pain, thickening of the zone involved and the characteristic numbness of the chin due to compression of the mandibular nerve.
A specific problem is pathological fracture, frequently a first sign.
Pain in the temporo-mandibular region/joint is the main symptom when the condyle is involved.
Contrary to the numb chin (to be discussed further), mandibular neuralgia is a non-specific finding indicating a possible involvement anywhere in its course of the mandibular nerve from the foramen ovale on. This is usually accompanied by serous otitis media, weakness and atrophy of the masseter and progressive and permanent pain. Perineural extension from oral tumors, particularly adenoid cystic carcinoma of the salivary glands, but also mucosal and melanoma have been involved. CT and MRI are very helpful to delineating and examining the infratemporal fossa (Marsot-Dupuch et al.).

The Numb Chin'

A very frequent symptom of involvement of the mandibular nerve is the numb chin. While mandibular osseous involvement is the main reason for this symptom, any involvement of the nerve along its course from the ganglion of Gasser can result in this situation (table 7.35). Depending on the accrued patients, mandibular involvement will account for 60 to 80%. Less frequent are leptomeningeal carcinomatosis; about 20%. In at least 30% of the patients it will be the first sign of an unknown cancer, but in another 30% it will be the first announcement of the first metastasis.

Table 7. 35 - The Numb Chin - Causes

Metastasis to the Mandibular Bone
Perineural spread of any oral or pharyngeal cancer
Metastasis within the Pterygo-Maxillary Canal
Bony Metastases to the Cranial Base
Leptomeningeal Carcinomatosis

Diagnosis

In a pateint known to have been treated for a malignancy, the likelihood of metastases should always be considered. The difficult cases are the first presentations, where a biopsy will bring the diagnosis of metastatic disease, possibly pointing to the primary. An important point is that the primary has apparently always been found.
Radiology and other imaging methods are helpful but aspecific, but a negative radiology or scintiscan should notlead to the patient being dismissed.

Leptomeningeal carcinomatosis is always progressive and other cranial nerve palsies will become apparent. However as Burt et al. have pointed out, the involvement of the dura can be 'patchy' with normal results from CT-scan and CSF cytology, causing an isolated neuropathy.
When no other cranial nerve is involved, a mandibular problem is much probable, but it is not uncommon that it will be apparent only some time later. The incisive nerve continues its course along the inferior alveolar canal beyond the foramen mentale and innervates the lower incisive teeth. If this site is also numb, it is very probable that the involvement of the mandibular nerve is distal. When the lesion is more central, a disso-ciation of sensory modalities is possible and the dental sensation should be spared (Lossos et al.).

Routes of entry to the Mandible in Contiguous Invasion

Several authors have addressed the problem of contiguous invasion from intra-oral cancers (fig.7.14).
In a study of 40 mandibles, MacGregor et al. concluded that squamous cell cancers enter the medullary cavity through the upper border of the mandible, either at the occlusal ridge ar in combination with penetration of the buccal or lingual plate. The penetration is likely to happen through anatomic foramina, but not frequently through cortical bone defects in the edentulous alveoles.

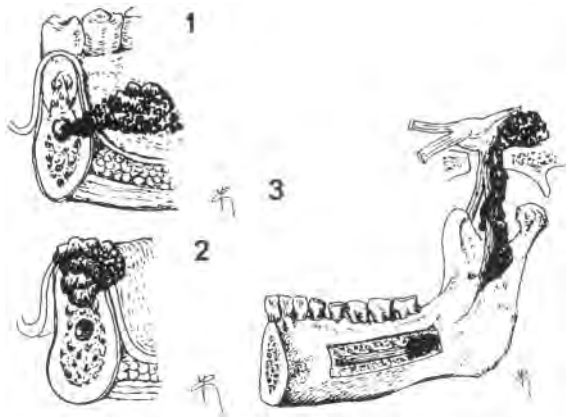


Fig. 7.14 - Some modalities of the invasion of the mandible. 1. from the buccal mucosa; 2. from a gingival tumor; 3. perineural invasion along the mandibular nerve.

That the mechanism is more intricate was shown by Slootweg et al. The tumor spread is not likely to occur through periosteal lymphatics, but via an advancing front. They have discerned two different types of mandibular bone involvement.
The first is characterized by a relatively sharp tumor-bone interface, where the bone border exhibits signs of active resorption giving space to the invading tumor. The resorption goes sometimes as far as the mandibular canal. This may result in the compressing and invasion of the neurovascular bundle.
The second pattern is a diffuse infiltration into the bone, with destruction and tumor spreading into cancellous spaces. The lingual or buccal plate is sometimes perforated. Further studies have determined that the periodontal ligament does not play a major role in the tumor spread. The larger the size of the tumor, the more the mandible is involved. The route of entry is entirely dependent of the position of the tumor relative to the bone. It is obvious that gingival cancers will almost immediately invade the bone, whereas tumor of the floor of the mouth must reach a particular size before the invasion.

Huntley et al. have stressed that the importance of two factors. The first is the reduction in height of the alveolar crest in the age group concerned, when most of the teeth may be lost. This shortens the distance that a carci-noma of the floor for example needs to reach the alveolar crest. Secondly, the structure of the cortical bone of an eden-tulous part of the crest is incomplete andthe more like a cicatricial plane above the alveolar cavity.

In a study of a small number of excised mandibles,

Lukinmaa et al. concluded that the bone involvement will depend more on the location rather than the proximity to the mandible and the size of the tumor. They also noted that a clinical fixation to the bone is not a prerequisite for bone involvement, as histologic invasion may be found without this situation.

Very recently, a detailed study of the anatomical foramina at the medial surface of the mandible was reported (Fanibunda et al.). Additionally to the known foramina, several other ones were found, and this may explain the possible tumoral invasion.

METASTASES to the SCAPULA

This metastatic site is almost not addressed in the literature. Samilson et al. found 12 literature cases in 1968, but added 23 of their own cases, demonstrating that this site is underreported. Metastatic disease in this bone does not cause serious troubles compared with spine or mandible localisation, and is probably not looked for during autopsies.
From this point of view the data from Jacobsen et al. taken from their hospital files, are particularly telling (table 7.36).
While in the first review by Samilson, the majority of cases reported were from breast cancer, recent data (or at least the published data) mainly concern kidney carcinoma. In total, there have been two type 1 metastases published from a kidney cancer, one from an esophageal (Cuomo et al.) and one from an hepatocellular carcinoma (Zeller et al.). There is almost certainly a bias in the publication towards uncommon cases, while several other cases such as from breast cancer go unnoticed in the clinical picture of diffuse metastases.

Table 7. 36 - Metastases to the Scapula
Incidence at Norwegian Radium Hospital (1980-1990)
Data of Jacobsen et al. 1994

	N cases	N receiving RT for scapular metastases
Kidney	289	12 (4%)
Prostate	441	3 (<1%)
Breast	1652	20 (1.2%)

Table 7.37 - Metastases to the Scapula
Primaries
Literature review by the author

Breast	22	One case each of
Kidney	30	Stomach, Soft palate,
Thyroid	4	Melanoma, Synovioma(?)
Bronchus	3	Colon, Cervix Uteri
Liver	2	Unknown (adenocarcinoma)

Our literature review points to a high number of renal cell and breast cancer patients (table 7.37).
One aspect of scapular metastases is that they are frequently solitary.
The presenting signs are local pain and swelling, some having been labeled as 'arthritis'. Diagnosis can be obtained with fine needle biopsy, while CT is the imaging method of choice.

SPINAL METASTASES

Pathways of Metastases to the Vertebra

The spread of metastatic cells to the vertebra is either hematogenous, or by contiguous invasion from adjacent tumors such as metastatic lymph nodes. The latter are however not true distant metastases.
The hematogenous spread is either arterial or venous via the prevertebral plexus of Batson.
In the most recent decades, a number of studies have been carried out shedding more light on the mechanism of invasion within the vertebra.

The arteries and veins of the spine have different anatomic distributions within the vertebral bodies (fig.7.15).
When the cells arrive through the arterie, they probably lodge in the end arterioles and sinusoids near the vertebral end plate. Venous metastases, however, spread into the vertebral bodies in retrograde fashion against the unusual venous flow. The cells most probably first arrive in the posterior central portion near the basi-vertebral veins (Yuh et al.).

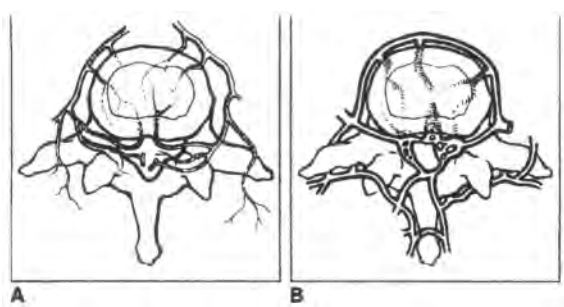


Fig. 7.15 - Arterial (A) and venous (B) vascularisation of the vertebral bodies. Hematogenous spread occurs most probably via the posterior and anterior vessels (Algra et al., with permission)

Metastases in the vertebral bodies correlate with the abundant vascularization in the red marrow. The rich blood supply in the pedicle-transverse process region explains the early metastasis at that site (Kricun).

Progressive destruction leads to erosions, defects and ultimately fractures. This gives rise to an axial failure of the vertebra, at first easily overlooked, as the dense framework of the apophyseal rings remain intact. A substantial loss of tissue within the body can be compensated by a swelling expansion of the discs, herniating into the bodies *as* an intrinsic fracture. The annular lamellae of the disc rupture and flow into the vertebral body. Defects of up to 50% of the body can be filled up (Jonsson et al.).
When CT evaluation of the involved vertebra is done,

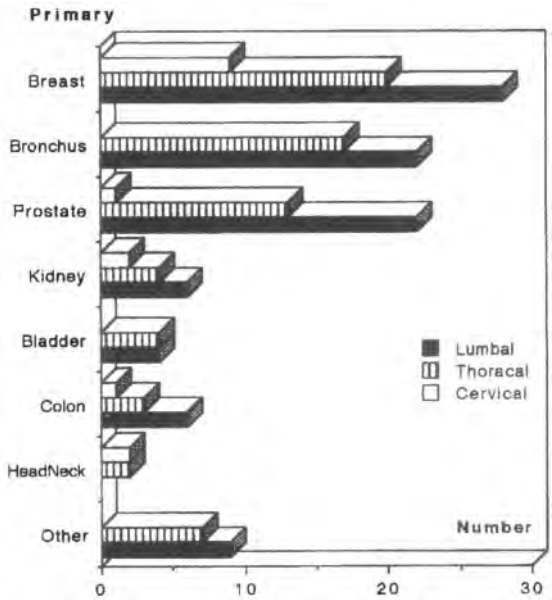


Fig.7.16 - Distribution of spinal metastases according to segment for different primaries (drawn from data of Schaberg et al.).

the posterior portion is the site most frequently destroyed (Algra et al.; Yuh et al.; Fujita et al.). This supports the claim that metastases start in the bone marrow of the posterior region. The different ligaments serve as barriers to tumor progression. The weakest barrier is the posterior ligament, which is gradually destroyed by the tumor at the point of perforating vessels (Fujita et al.).

It is not known wether that tumor cells spread via an arterial or via a venous route, but both ways are probably involved in every patient.

Spread to the adjacent vertebrae can occur either from the edge of the body beneath the longitudinal ligament or through the paraspinal muscles to the neighbouring lamina.

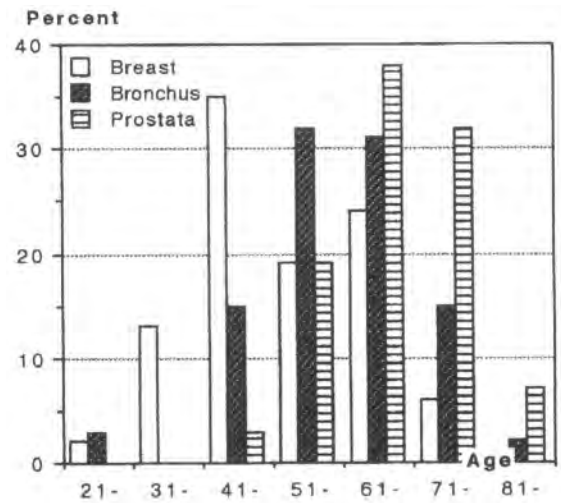


Fig.7.17 - Age at 'spinal uptake' for different primaries (N=150). Drawn from data of Morishita et al.

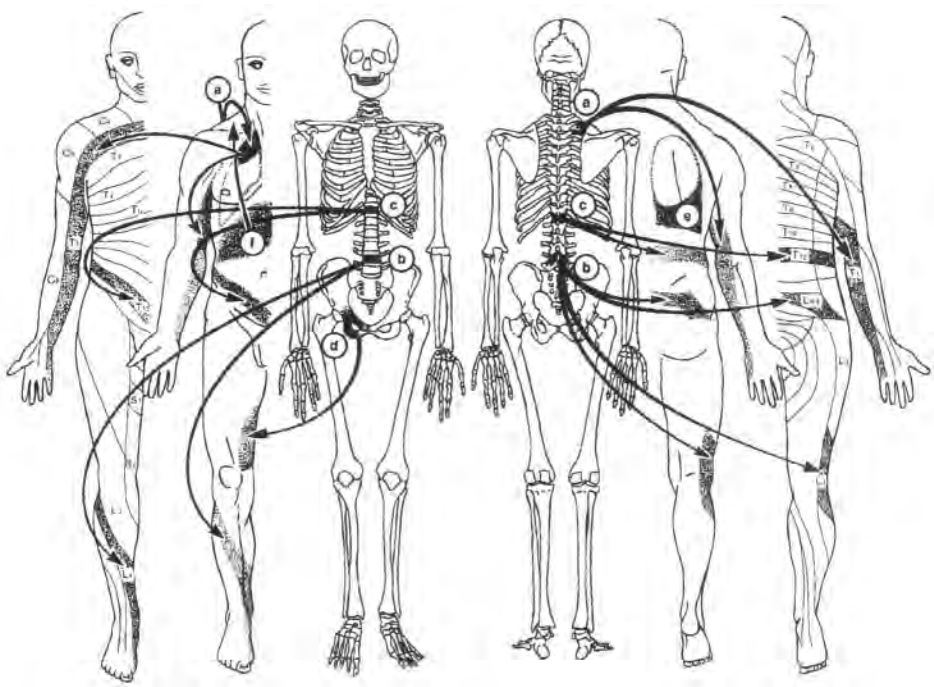


Fig. 7.18 - Schematic outline of some frequent irradiating syndromes misleading the non-alert clinician. a. Pancoast syndrome, irradiating to the hand; b. Compression of lumbar radicular nerve with pain irradiating to the lateral leg; c. Compression of thoracal nerve, with pain irradiating to the abdominal wall; d. Osteolytic zone irritating the obturatorius nerve, with pain irradiating to the internal side of the knee; e. Pleural effusion irradiating pain to the shoulder; f Liver metastases at the upper pole irradiating pain to the shoulder.

True involvement of the disc is hardly discussed in the literature, but apparently rarely observed. Reviewing 25 spines from prostatic cancers, Resnick et al. was none, although the pathology observed was always osteochondrosis or Schmorl's nodes, while involvement of the disc always was associated with invasion from neighbouring bony tumors.
There is some correlation between the level involved and the type of primary, but there are only scant data, so that firm conclusion cannot be drawn. Fig.7.16 shows the data of Schaberg et al., indicating that pelvic tumors have proportionally more lumbar metastases.
Thoracal tumors such as breast and bronchus have, however, clearly more metastases within the lumbar spine. Similar data were obtained by Morishita et al.
The latter authors also examined the influence of age on the incidence of spinal metastases, as determined by nuclide scintigraphy in different primaries. Breast cancer patients with sînal metastases were obviously younger, with a peak incidence at 41-50, while it was later in bronchial cancer and for prostate cancer (fig.7.17).

Symptomatology

Spinal metastases have a variable symptomatology, depending on the extent of the vertebral involvement, the site within the vertebra and the segment of the spinal column.
The part of the vertebra destroyed will have an impact on the stability of the spinal column. When the destruction is more at the external border, the neighbouring muscle will go into contracture to stabilize and will give a more local pain. At the posterior border the risk of instability will involve a possible progressive compression of the spinal cord, with its own clinical picture as discussed later. Other metastases will impact on the radicular nerve with their typical radicular and/or referred pain depending on the spinal segment.

The site where the patient reports his pain can be very misleading to the non-alert clinician, leading to unappropriate measures as faulty imaging procedures or inadequate treatments, postponing the diagnosis. A selection of the most important of these radicular and referred pains is shown in fig.7.18.

Imaging

The different imaging modalities, as will now be briefly discussed, have a sensitivity that correlates with the progressive destruction of bone (fig. 7.19). They are not mutually exclusive and some can add information.
Plain films have the limitation of low yield in depicting bone metastases when only located within the bone marrow. A resorption of more than 50-60% of the trabecular bone is the threshold at which visualization of bone involvement is possible.

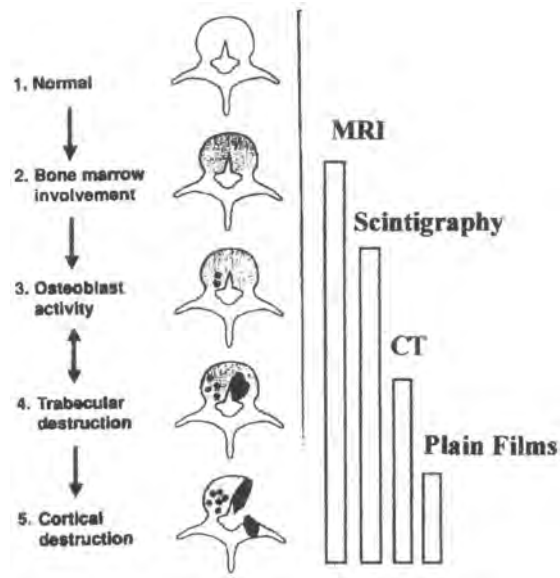


Fig.7.19 - Possibilities of the different imaging methods according to the stages of bone destruction by metastatic involvement (Modified from Algra).

Radionuclide scintigraphy is very sensitive as it detects any altered local metabolism with reactive enhanced osteoblastic activity. As little as 5 to 10% change in normal bone is enough to obtain a 'visible reactive' focus. The interpretation is hampered by its aspecificity and must take other factors into account.
CT can image subtle cortical and trabecular destruction. However, it is unable to detect the early stages of spinal cord compression.

The superiority of MRI lies in its ability to detect minimal changes in the bone marrow, be it fatty changes or modifications to tumoral invasion. As it can also visualize soft tissue and the slightest modification made to it, it is extremily important in the early detection of spinal cord compression, be it due to vertebral fracture or any epidural tumoral involvement or invasion. The MR appearance of the bone marrow can be divided into four distinct patterns (Algra) (fig.7.20).

Since metastases usually have a low signal comparable to that of water, they are easily discernible in the yellow 'fatty' marrow in elderly and some adult patients, but barely in the red marrow of children and young adults. A 'normal' fatty signal rules out metastases.
Sclerotic metastases behave like lytic metastases on MRI. Very pronounced sclerosis is rarely hypointense on all sequences.
Collapsed vertebrae must be differentiated from osteoporotic vertebrae. A large number of lesions will be more indicative of metastatic process. A high signal of the vertebral body on gradient-echo images due to trabecular destruction is often seen in metastases (Vanel et al.).

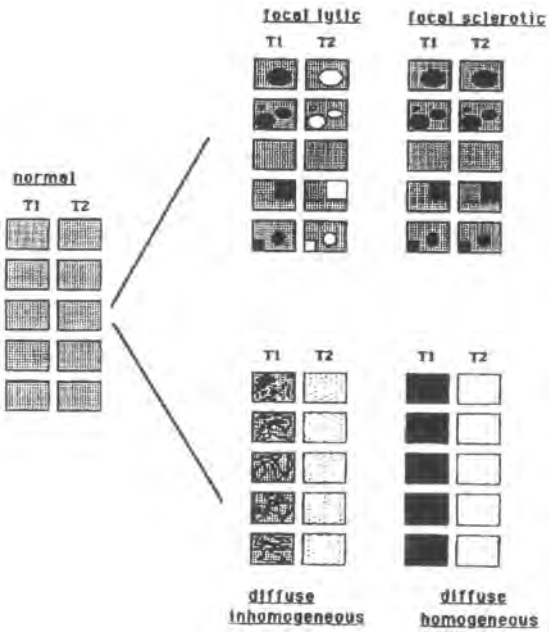


Fig.7.20 - The four MRI appearance patterns of bone marrow in cases of metastatic involvement (Algra, with permission)

Table 7.38 - Metastatic Bone Marrow Involvement
Features of MR Imaging in the detection
of Malignancy and of Spinal Cord compression
Modified from Algra

Feature	Appearance in Malignancy
Abnormal Signal Intensity	Focal within body
	Involvement of whole body towards pedicle a. posterior
High SI on T2W around lesion	Yes
Bright disc on T1WSE	Yes in diffuse metastases
Vertebrate collapse	
acute	Abnormal SI of entire body, pedicle and posterior part
chronic	Abnormal SI of entire body
Cortical destruction	Present
Destruction of disc	Rare
Convex posterior border	Present
Soft tissue extension	Present
Status of other vertebrae	Frequently also metastatic
Gadolinium enhancement	Globular
Gadolinium dynamic	Slope >30%
Basivertebral vein	May be absent
Number of Lesions	May be multiple
Additional Findings	Lymphadenopathy
	Primary Tumor
	Liver, lung, brain metastases
	Leptomeningeal metastases

Focal lytic metastases with focal area show decreased signal intensity on T1W images and an increased T1/T2* signal. The other differences are in table 7.38. In diffuse patterns of involvement, the marrow will show a low signal, becoming more homogenous on further destruction and progressively more bright on T1/T2*. In the differentiation of images of metastases from other bone marrow pathologies (table 7.39), these few features may provide useful clues.

Table 7.39 - Metastatic Bone Involvement
MRI appearance patterns (from Algra)

	at T1W	at T1/T2*W
Focal lytic	decreased	increased
Focal sclerotic	low intensity	low intensity
Diffuse inhomog.	low signal	high
Diffuse homgen.	low homogen.	high bright

Metastases to the CERVICAL SPINE

Metastases to the cervical spine are much less frequent than in the other segments.

Primaries

In table 7.40 we show the primatries involved in 8 small series, and have compared them with the literature review by Nakamura et al. Forty percent of the primaries are breast cancer. It is striking that two of the cases we found involved the rare lacrimal gland cancers.

One of the sits singled out has been the involvement of C2. Lally et al. (1977) reported on 6 cases, all from breast cancer. We are not aware of more recent reports on this site, except a study of malignant fractures of the odontoid process by Sundaresan et al. They collected 18 personal patients, of whom were 11 female breast cancer patients. The others were from various primaries such as colon, bronchus, nasopharynx, sarcoma and myeloma. The symptomatology is dominated by high neck pain irradiating to the occiput and limitation of rotary movements. Some also had radicular symptoms to the upper extremities, probably because of other vertebrae involved.

Table 7.40 - Metastases to Cervical Spine
Primaries involved

	Literature	Nakamura(°)
Breast	37 (40.2%)	39 (43.3%)
Bronchus	12	11
Prostate	8	7
Kidney	5	5
Head and Neck	3	3
Liver	3	--
Thyroid	2	5
Stomach	1	4
Colon	2	3
Uterus	2	--
Urin.Bladder	2	1
Melanoma	2	--
Lacrimal gland	2	--
Various	3(')	6
Unknown	5	5

(') one case of ovary, salivary, gallbladder
(°) we excluded 11 myeloma

According to Rao et al., the mean time from primary

diagnosis to diagnosis of cervical spine metastasis was 29 months. It was the shortest for bronchial cancer (2.2 months), for the prostate 18.6 months, but relatively long for breast cancer (89 mo). Isolated cervical spine metastases are rare; about 10% of the patients with cervical metastases. The lower cervical vertebra are in general the most frequently involved.

Symptomatology

Pain is the predominant symptom. It is reported in about 90% as localized and with unremitting discomfort. Pain may be unilateral, progressively worsening and not related to activities. Sleep interruption is common.
A sudden onset with minimal or no trauma might indicate a pathological fracture.
Neurological dysfunction may present with variable intensity and rapidity of onset. A relatively uncommon condition is a cervical radiculopathy from tumor metastasis in the epidural space. The pain will then described as a burning, dysesthetic type pain radiating in a specific dermatomal pattern, suggesting root involvement.
Spinal cord compression with symptoms of myelopathy may develop and be the presenting feature of cervical metastatic disease. This is more common in the subaxial area than in the atlanto-axial region.
When the anterior epidural space is involved, motor deficits are often the initial presenting features.
With progression, long-tract signs and a myelopathic hand syndrome with intrinsic hand atrophy can be observed. In most series up to 10% of the patients are asymptomatic and only diagnosed at staging procedures (Jenis et al.).

Diagnosis

In most skeletal surveys, at least with radioisotopes, imaging of the cervical spine has not been adequately studied. Moreover slight hyperactivity in that region is normal, leading to false positives. Profile images are almost never obtained.
Plain radiology is no longer indicated in cases where metastases are suspected. CT is the imaging method of choice, while in cases involving compression, MRI is of the utmost importance.

SPINAL CORD COMPRESSION

This most dreaded and poor prognostic situation is caused by the invasion of the epidural space from an involved vertebral body, with further destruction of the adjacent vertebrae resulting in loss of stability of the spine and knicking of it with resulting spinal cord compression.
The spinal epidural space is a true space. It is delineated by the periosteal lining, the bony spinal canal and the dura mater covering the spinal cord and cauda equina. It extends laterally for a short distance through the intervertebral foramina along the spinal nerves.
The space is composed of areolar tissue, connective tissue and an extensive network of veins. In the lumbar spine it contains the paravertebral plexus of Batson.
This venous plexus was discussed above.
There are no lymphatic channels nor lymph nodes within the epidural space. The regional nodes of this space are the prevertebral nodes (Chamberlain et al.).

Pathways of Involvement

There will usually be direct extension from an involved vertebra as what currently happens with cancers prone to metastasize in bone. Other tumoral processes such as lymphoma, neuroblastoma and extensive prevertebral nodes invade the space by ingrowth of the tumoral mass through the intervertebral foramina.

The involvement of the epidural space is favored by the bidirectional flow within the internal vertebral plexus (Batson), the direct communication with the thoracic and lumbar and pelvic venous system and the life-long active 'red' bone marrow (fig.7.21).

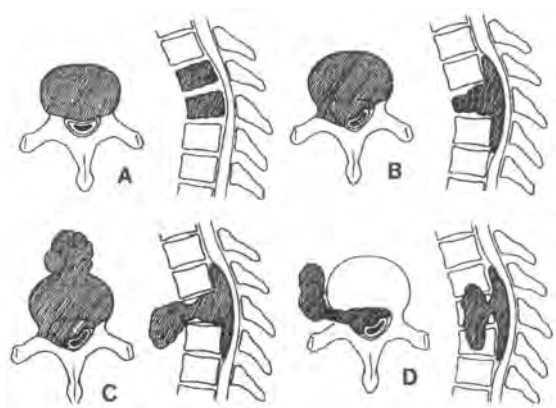


Fig. 7.21 - The four most important causes of neurological manifestations through spinal metastases: A.: Vertebral collapse; B. Vertebral involvement and epidural extension; C. Vertebral destruction and extension of tumor into epidural and prevertebral space; D. Extension from a paravertebral metastatic node into the vertebra and intraluminal space (from Constans et al., with permission)

Pathology

The majority (85%) of the epidural tumors arise in the vertebral body, invade the epidural space anteriorly and remain largely anterior to the spinal cord. Some extradural metastases will be located either posteriorly or anteriorly.
Multifocality is usually not discussed, as the most destructive site will normally determine the presenting level. It has been demonstrated, however, that in 16 of

the 54 patients with epidural metastases, the myelogram disclosed more than one epidural metastases, located at a lower level. This occurred with all tumor types (VanderSande et al.).
According to Helweg et al., multiple lesions were much more common in bronchial cancers (table 7.41).

Table 7.41 - Spinal Cord Compression
Lesion Multiplicity (N=107)
Data of HelwegLarsen et al.1995

Primary	Single	Multiple
Breast cancer	62	38%
Prostate	55	45
Bronchus	82	18
Other	64	46
Overall	65	35

In 100 patients, there were only 3 metastases at the cervical region, 76 in the thoracal region and 21 in the lumbar segment (data of Livingston et al.). They remarked that the segment most frequently involved was between T4 and T11 (fig.7.22). There is no obvious reason for this, but it must correlate with the frequency of vertebral involvement and the segment which is the most involved in the weight-bearing forces. Other reports have no accurate data concerning the different levels involved.

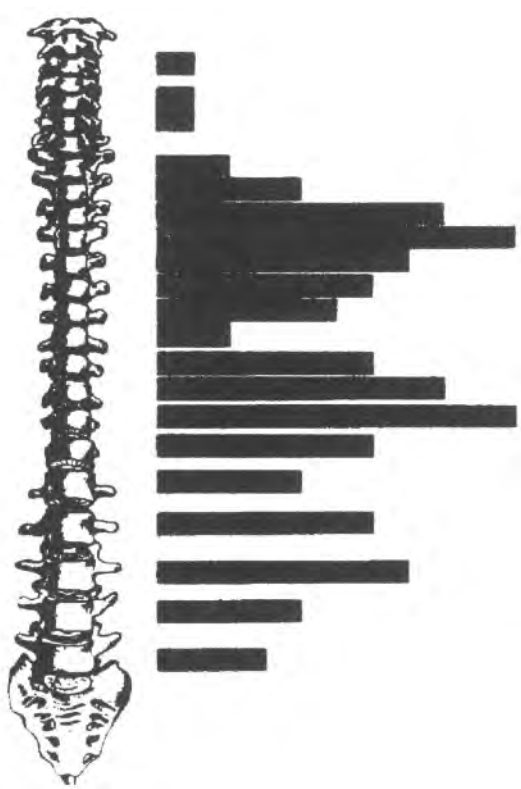


Fig.7.22 - Relative site distribution of compression-producing metastases along the spine. Data from 100 patients, Livingston et al. 1978 (with permission)

Other data report a majority of 70% to the thoracal vertebrae, 20% to the lumbosacral and 10% to the cervical. At least one third of the patients have multiple levels involved, but the more sensitive the imaging method is, the more likely it is up to 85% will have multiple level involvement observed (Grant et al.).

Pathophysiology

For the patient, compression of the spinal cord results in sequellae due to vascular compromise of the spinal cord. The epidural compression damages the cord either by direct compression or by vascular ischemia. Venous congestion will add to the arterial obstruction and lead to hemorrhages, edema and atrophy due to demyelinization.

Primaries

As with most skeletal metastases, the osteophilic tumors, breast, bronchus and prostate are the most frequent cause of spinal cord compression, in about three quarters of the cases. There is some correlation between the location of the primary and the spinal segment involved (table 7,42).

However, every primary, be it head and neck cancer or prostate can result in a metastatic site at any level. Of 5 head and neck cancers with spinal cord compression, 4 had the metastatic site below Th.6 (Ampil et al.).
Reviewing the literature, Grant et al. observed that in a general hospital, 47% of the patients presenting with spinal cord compression were not known to have a primary cancer, while it was only 10% in a tertiary cancer hospital. When unknown, the primary was found in about 70%, with half of them a bronchial cancer.

The incidence of spinal cord compression in pediatric oncology is estimated at 3%. They mainly involve the different types of sarcomas and further the typical pediatric malignancies such as neuroblastoma and Wilms's tumors (table 7.43).

Table 7.42 - Spinal Cord Compression
Primaries in 153 cases
Data of Helweg-Larsen 1996

Primary	Cervic.	Thorac.	Lumbar	Total
Rhinopharynx	0	1	0	1
Thyroid	0	1	0	1
Breast	4	33	19	56 (36%)
Bronchus	3	23	1	27 (18%)
Mesothelioma	0	0	1	1
GIT	0	8	3	11
Kidney	0	6	0	6
Prostate	0	29	14	43 (28%)
Sarcoma	0	1	3	4
Melanoma	0	0	3	3
TOTAL	7	102	44	153

Table 7.43 - Spinal Cord Compression in Children
Primaries concerned (N=551, 1989-1995)
Modified from data of Kebudi et al. 1998

Primary	N	N epid	%
Sarcoma	149	7	4.6%
Rhabdomyosarcoma	65	1	1.5
Osteosarcoma	45	4	8.8
Ewing's sarcoma	39	2	5.1
NonHodgkin Lymphoma	38	2	5.2
Neuroblastoma	30	3	10.0
Wilms' tumor	32	1	3.1
Germcell Tumor	24	2	8.3
Other	278	none	
ALL	551	22	3.9 %

Klein et al. observed spinal epidural metastases in 112 or 5% of the 2,259 children treated for solid malignant tumors. The highest number concerned Ewing's sarcoma and neuroblastoma, while the incidence was the highest in the former group.
When one considers however the different types, the incidence of spinal cord compression is the highest in the group of neuroblastoma and osteosarcomas, with an incidence of about 10%.

Time of Occurrence

In the large majority (80%) diagnosis of a primary neoplasm will already have been made. In the remaining cases, the diagnosis is either made when the cord compression is found or even later. Data were provided by Bach et al. (table 7.44).

Table 7. 44 - Spinal Cord Compression
Time Interval between
Diagnosis of Primary and Cord compression (N= 398)
Data of Bach et al. 1990

			Primary known		
Tumor	N	Mean	Before	Sim.	Later
Prostate	74	1.7yrs	82%	11%	7%
Bronchus	72	0.5yrs	65	31	4
Breast	54	4.6yrs	98	2	--
Kidney	38	2.2yrs	79	11	11

In thirty-one percent of the bronchial cancers, diagnosis of the primary is made at the presentation of cord compression. In between 5 to 10% the primary is found only after presentation of the spinal cord compression syndrome, in kidney cancers up to 10%.
In general, the time interval is largest in breast cancer. Interesting data on the time interval were recently published by Helweg-Larsen et al. in relation to 153 consecutive patients. As expected, relatively short intervals for bronchial cancers were common, while they were much longer for breast cancer (fig. 7.23).

Symptomatology

The clinical picture of metastatic spinal cord compression has been uniformly reported as involving pain, weakness, sensory loss and autonomic

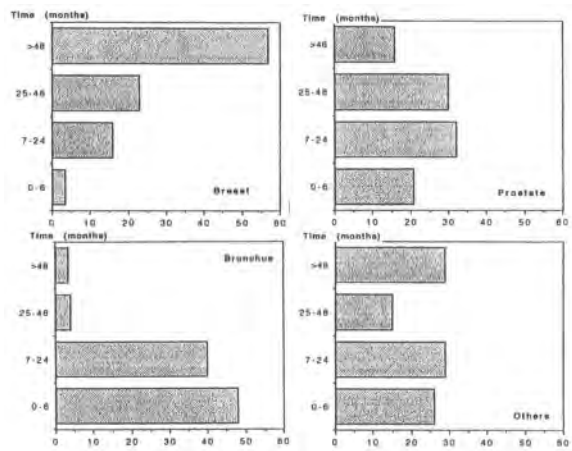


Fig.7.23 - Time-sequence in the occurrence of spinal cord compression for breast, prostate, bronchial and other cancers. Drawn from the data of Helweg-Larsen et al.

dysfunction.
Approximately 90% of the patients present with central back pain.
The clinical picture is remarkably uniform, whatever the cause and involved primary. It can be divided into two stages or phases (Ratanatharathorn et al.).

1. The prodromal phase: the patient presents with pain with or without radicular pain preceding other symptoms. The local pain generally corresponds to the site of the lesion. Radicular pain may aid in the localizing the site, but it occurs less frequently.
2. The compressive phase: in spite of the long duration of painful symptoms preceding neurologic deficit, 15% still present with paraplegia.

The pain is due to

- pressure or infiltration of pain sensitive structures such as spinal nerve roots, dura mater, annulus fibrosus of the disc and the anterior and posterior lon-gitudinal ligaments.
- stretching of periosteum by direct pressure from tumor
- micro and macro-fractures of the bone.

The pain is generally more severe in extra-dural or extra-medullary tumors than in intramedullary or intraspinal tumors.

In the early stages there is more motor disability than sensory, because of the anterior compression of the spinal cord. It is present in 75% of the patients at diagnosis. Autonomic dysfunction occurs later but can be the sole neurological deficit.
Numerous articles have described the symptomatology at different stages. In our view, the data from a meticulous study in 398 patients, provides sufficient illustration (Bach et al.).
Looking at the degree of the clinical evolution is considered according to the classification proposed by Constans et al., it will be seen that about 20% are

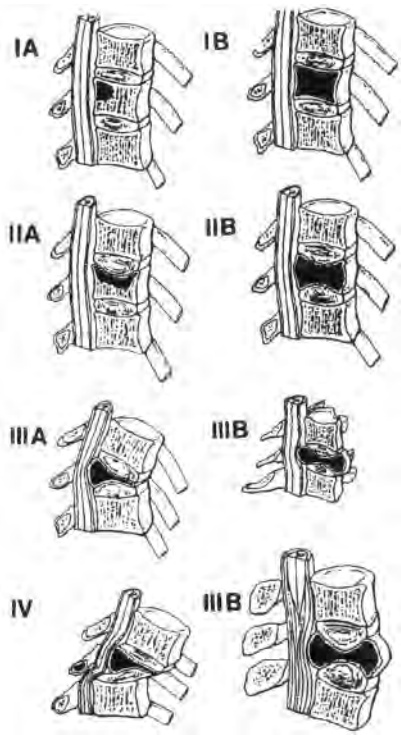


Fig.7.24 - The stages of vertebral deformity as described by Asdourian et al. :IA: Metastasis involves a portion of the vertebra; IB: Complete replacement of bone marrow; IIA: Deformity of one vertebral plate; IIB: Compression of ver-tebra results in 'ballooning'; IIIA: Collapse results in in-creased kyphosis; IIIB: Symmetrical collapse; IV: Trans-lational deformity (with permission)

Table 7. 45 - Spinal Cord Compression
Symptomatology at Presentation in 398 patients
Data of Bach et al.1990

Symptoms		
Pain	Radicular	47%
	Local Back	36%
	No pain	17%
Motor Signs	Failing Control	67%
	Limpness, weakness	27%
	No symptoms	6%
Sphincter Dist	Severe	47%
	Moderate	18%
	No symptoms	35%
Signs		
Sensitivity	Level established	61%
	Not established	29%
	Normal	10%
Motor Function	Paralytic paraparetic	64%
	Mild deficit	32%
	No deficit	4%
Sphincter Dist	Retention	47%
	Moderate	22%
	No symptoms	31%

still in what is viewed as an early phase (table 7.45), An anatomically and radiologically derived staging of the vertebral destruction resulting finally in spinal cord compression was proposed by Asdourian et al. Stage III is obviously the one most frequently encountered in orthopedic practice (Fig.7.24),

Table 7.47 - Spinal Cord Compression
Grading of patients at diagnosis (N=600)
Data of Constans et al. 1983

Grade	Clinical Characteristics	N	Incid.
1	pain or minor neurological symptoms normal spocial & professional activities	56	9.33%
2	mild neurological symptoms, normal social life but profession interrupted	82	13.67
3	moderate neurological symptoms (paraparesis, sphincter problems, columnar pain), active life impossible	203	33.83
4	serious neurological syndrome (paraplegia, complete sphincter deficit)	209	34.83
5	medullary syndrome if spinal transsection	50	8.34

Diagnosis

Clinical awareness is very important at both early stages and later so that treatment can start early before the paraparesis becomes flaccid.
The main cause of delay is failure to diagnose spinal cord compression and failure to investigate and refer urgently. In the course of 24 hrs the situation can progress to an irreversible paraparesis and neurological picture. Patients must be referred urgently to an oncology center.

Imaging will show spinal / vertebral involvement,but myelography will determine the level. MRI is much more sensitive in early stages and important for prompt diagnosis. Moreover, it can overcome both the invasiveness and time-consuming myelography procedure.

MRI will demonstrate the vertebral body metastasis, a para-vertebral tumor, the intramedullary metastases, the cranial and caudal extent of the tumor, the degree of subarachnoid compression and the distinction between benign and metastatic vertebral body collapse. Contrast is usually not necessary and because of the risk of multifocality, the examination should include the entire spine.

When one reviews charts of patients presenting with signs suspiciously of spinal cord compression, the frustrating thing is that, while in a small number, the symptoms will be relatively clear, no cord compression will be found and vice-versa. Barnat et al. have tried to identify some factor groups which will permit to increase the diagnostic capability of the neurological examination. They were, however, unable to select a useful set. Their comparative data are shown in table 7.47.

How significant the differences might be, it remains difficult to detect incipient spinal cord compression. If there is any doubt, MR imaging should be ordered. An accurate history taking, prompt evaluation of the history of pain and other neurological symptoms and

signs such as weakness and radicular pain are valuable elements contributing definitive judgment.

Table 7. 46 - Spinal Cord Compression
Comparative analysis of definite diagnostic Groups
Modified from Bernat et al.

Symptoms	Compressio	NO compression
Any Pain	97%	66%(*)
Local pain	43%	32%
Radicular pain	13	18
Local and radicular	43	15(*)
Weakness	77	58(*)
Numbness	47	41
Sphincter probl	39	34
Signs		
Paraparesis	85	59(*)
Sensory level	74	41(*)
Hyperactive Reflex	69	54
Extensor Plantae	45	23(*)
Decreased recta tone	35	14(*)
Back or neck tenderness	60	30(*)

(*) significant at P<0.05)

Differential Diagnosis

In order to initiate adequate treatment, the following pathologies should be considered, when the symptomatology described presents (Raranatharathorn et al.).

1. Disc herniation, readily seen on myelogram and corresponding to the level of intervertebral discs;
2. Vascular diseases, either hemorrhagic or infarction of the spinal cord, or even abdominal;
3. Infectious processes such as pyogenic epidural abcess, tuberculous radiculo-myelitis, Potts' disease, and others;
4. Benign neoplasms of the spinal column, the spinal cord or intrarachidial such as chordoma, meningioma, neurinoma, chordoma and others;
5. Malignant primary tumors of the spinal column such as osteosarcomas or secundary processes of the spinal canal such as the leptomeningeal carcinomatosis;
6. Paraneoplastic syndromes as necrotizing myelopathy, carcinomatous subacute poliomyelitis;
7. Neurologic disorders such as multiple sclerosis, amyotrophic lateral sclerosis;
8. Radiation myelopathy diagnosed per exclusion;
9. Transverse myelitis of unknown etiology.

METASTASES to the STERNUM

Sternal metastases have received scant attention in the literature. It is not a rare localization, at least in the evolution of breast cancer.
The sternum can be involved in two ways: firstly by the hematogenous route for the distant cancers, and secondly by neighbouring infiltration from a recurrent breast or other thoracic wall tumor. Not all breast cancers will invade the sternum by this route.
Invasion of the sternum from retrosternal anterior diaphragmatic nodes has been observed.

They are frequent in cases of diffuse bone metastases in breast cancer patients. An autopsy study in 415 oncology patients disclosed metastases in the sternum in 63, or 15% (Urovitz et al.). The large majority are in the corpus. The most cited primary was breast cancer and melanoma (more than 25%) , but kidney and stomach also account for a high number. The frequency in bronchial and gynecological cancers was lower, but still above 10%.

The latest report in the literature on sternal metastases dates back to1981 (Pirschel 1981) (table 7.48). As in two other small series, breast cancer is a major source, but kidney and thyoid tumors account for a large number, as a number of case reports show.

Table 7.48 - Metastases to the Sternum
Primaries Involved (N=77)
Series of Pirschel 1981

	Solitary	Generalized
Breast Cancer	20	30
Other various	17	20
Thyroid	14	
Kidney	5	
Bronchus	3	
Unknown	7	
Various	8 (no data)	

The occurrence of a large number of solitary metastases is striking. Several authors mention a particular type of sternal metastases, the pulsating type, described in connection with thyroid and renal cell cancers.
Strauss et al. reported a type 1 sternal metastasis for a renal cancer. They also had one from a cecum tumor and one from a uterine sarcoma.
Local pain is the major complaint. Bone scintigraphy is not specific, but the osteolysis is actually best demonstrated on CT.

METASTASES to the PATELLA

Patellar metastases are rare and rarely reported. They are much less frequent than primary tumors. The causes are open to conjecture, and may be related to poor vascularisation.
Breast and bronchial cancers are the most frequent, but cases from other osteophilic primaries have been reported, for example colon, esophagus, and stomach.
At least three reports concerned patellar metastases as first symptom of an unknown primary.
We have found only 26 publications on the subject, reflecting their rarity.

METASTASES to the LONG BONES

In spite of the hundreds of publications on metastases in the long bonesin which various techniques and results of different orthopedic treatments are described, there is a dramatic scarcity of data showing the distribution of the metastases within the bones.

Table 7. 49 - Metastases to the Long Bones
Correlation of primary with segment involved
Review by Bouvier et al. 1970

	Forearm	Hand	Leg	Foot
SupraDiaphragmatic				
Bronchus	8	41	2	9
Breast	14	15	17	12
Thyroid	2	0	4	1
Head and Neck	2	3	4	1
Parotid gland	0	4	0	0
Esophagus	0	1	3	0
InfraDiaphragmatic				
GIT(')	2	7	4	4
Uterus cervix	1	0	20	11
Endometrium	0	1	5	2
Vulva-Vagina	0	0	1	1
Ovaries	0	0	0	1
Kidney	2	4	7	6
Prostate	3	3	4	1
Urinary Bladder	0	1	2	1
Liver	1	0	0	0
OTHER	2	4	3	0
TOTAL	39	85	78	50

(') stomach 2, rectocolic 15

It has been stated that metastases in the skeleton of the lower limb are more frequent from primary sites below the diaphragm, while most of the metastases in the tibia and fibula were derived from cancers within the pelvic cavity, especially prostatic or vesical, and in women from endometrial cancers. Data are only available from a survey done in 1970 by Bouvier et al. (table 7.49). While these data do not completely confirm the hypothesis, the results for uterine cancers are striking.

We found some data comparing the incidence in humerus and femur (table 7.50), of surgically treated patients. While the shaft of the humerus is mainly involved, the proximal half is the most frequently involved site in the femur. This should be related to the respective vascularisation of the humerus and the femur, although both bones are vascularized all their length (fig.7.25).

A remarkable feature is that many pathological fractures are the first sign of the presence of a malignant tumor in the patient. However, only Katzner et al. have reported adequate data. About one tenth of the patients surgically treated or 31/254 (12.2%) had their fractures as first sign. The figure is the same for both the humerus and femur, with a remarkably high number of thyroid cancers (20%). A higher figure was reported by Miric et al. They found 18/83 lesions (21.6%) as first presentation of all metastases in the appendicular skeleton.

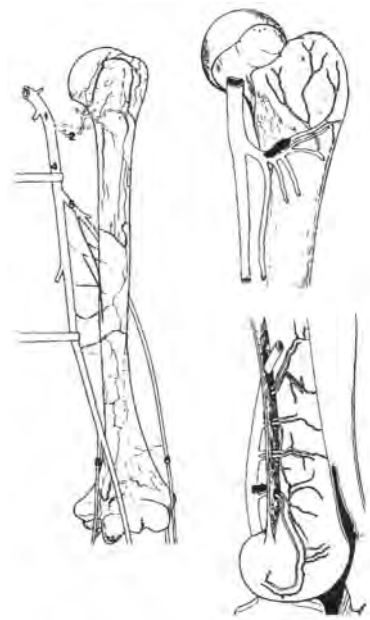


Fig. 7.25 - Comparative vascularisation of the humerus and the femur (from Menck et al., with permission)

One feature is that metastases within the lower arm and leg are much less frequent than those in the upper part of the respective limbs, but also less than those in the acral parts, as will be discussed further.

Literature data were collected by Bouvier et al. according to the primary involved (table 7.51). In 44 patients with humeral metastases 17 or 38.6% were from breast cancer. Twelve other tumors were responsible for the other cases, of which 7 were bronchial cancers and 4 renal cancers.

It should be noticed, however, that bronchial cancer is responsible for 50% of the hand metastases, while breast cancer is the main cause of metastases in the forearm. Nature is also choosy.

Table 7.50 - Metastases to the long Bones
Site of involvement within humerus and femur

Humerus	N=45 (data of Katzner et al.1979)	
	Neck of humerus	6 cases
	Shaft	33 (73%)
	Medial third in 50%	
	Supracondylar	4
	Multifocal destruction	2
Femur	N=306 (data of Haberman et al. 1982)	
	Acetabulum	2.9%
	Trochanteric	37.2
	Subtrochanteric	23.8
	Shaft	23.2
	Distal + supracondylar	13.4

Table 7. 51 - Metastases to the Limbs
Literature data reviewed by Bouvier et al. 1982

Primary	Forearm	Hand
Bronchus cancer	8	42 (50%)
Breast cancer	**18 (38%)**	**15 (18%)**
Gastrointestinal tract	2	8
Prostate	6	3
Kidney	2	4
Thyroid	2	0
Head and Neck	2	3
Skin	2	1
Parotid gland	0	4
Urin.Bladder	0	1
Uterus	1	1
Various	4	2
Total	47	84

METASTASES to the HAND and FOOT

These rare metastatic sites account probably for less than 1% of all skeletal metastases. They are probably underreported and they will go unremarked, autopsies hardly giving any attention to this site.
The big problem is that about 25% are revealing metastases and often misdiagnosed, as they can present with signs much more common to frequent pathologies of the finger or of the foot. A number of patients have many other metastases either in bone and/or elsewhere. The occurrence of these acral metastases is foreboding an infaust prognosis, but this will not be discussed here. They are undoubtedly all purely hematogenic.

The symptomatology is pain and/or swelling, but many masquerade as common acral pathologies such as osteomyelitis, panaris, traumatic sequellae with infection and many more.
Both genders are equally concerned. There are proportionally more hand metastases reported.
The most recent comparative literature surveys date back to 1987 for the hand (table 7.52) as far as the primaries are concerned and to 1983 (table 7.53) as far as the site of metastasis is concerned.
Only 25% of the foot metastases were from supradiaphragmatic tumors, while they amounted to 60% in the hand. A literature review on hand metastases by Nagendran et al. disclosed 33 cases of phalangeal metastases from bronchial cancer.
Our literature review after 1986 found 64 new cases of hand metastases, of which 8 were type 1 or revealing metastases (table 7.52) and 54 foot metastases. Fifty percent of the hand metastases originate from supradiaphragmatic cancers, and the same proportion has been found for the foot metastases.
In the hand, the large majority of the metastases are located in the phalanges (more than 80%), while only 17% in the foot. All fingers of the hand are evenly involved, while the distal phalanges are involved in half of the phalangeal cases (table 7.53).
This situation is different in the foot, half of the metastases located within the tarsals, with half of them in the calcaneum (table 7.54 and fig.7.26).

Table 7.52 - Metastases to the Hand and the Foot
Primaries -Literature Review

Primary	Hand(‘) N=196	Foot(“) N=94
SupraDiaphragmatic		
Bronchus	47%	15%
Breast	12.5	10
Larynx	1.5	--
InfraDiaphragmatic		
Kidney	11%	17
Prostate	2	4
Uterus	2	6
Rectum colon	5	17
Urinary Bladder	--	10
Ovary	--	2
Various		
Leukemia/Lymphoma	2	--
Sarcoma	4	--
Unknown	2	9

(‘) Libson et al.,1987; (“) Zindrich et al., 1983

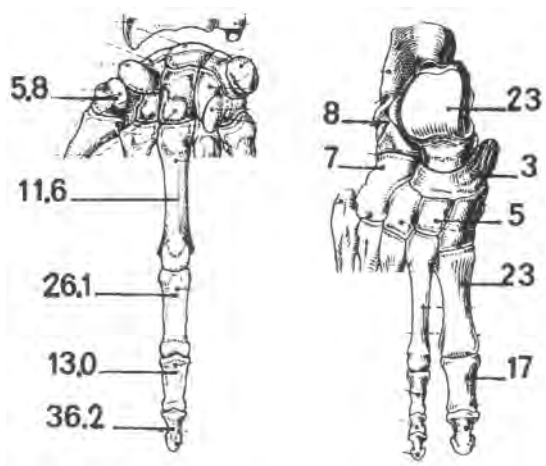


Fig.7.26 - Comparative incidence of the bone metastases in the different parts of hand and foot. Data by Chung et al. (table 7. 54) and by Zindrick et al. (table 7. 55)

Diagnosis

A definite diagnosis can be obtained by fine-needle or open biopsy or amputation. In cases of widespread metastases, the diagnosis will be obvious.
At radiology, the lesions will be osteolytic in more than 80%. Metastases from the prostate are generally sclerotic. Those of the breast, bladder and gastrointestinal tract may be lytic, mixed or pure sclerotic in appearance. Total destruction of the bone can occur at a late stage (Libson et al.).
Peculiar is that joints are almost never involved, possibly due to the cartilage barrrier, except in the later stages. This was stressed by Nagendran et al. who also point out that the periosteal reaction is usually absent and that the trabecular destruction leaves relatively normal surrounding trabeculae.

Table 7. 53 - Metastases to the Hand and the Foot Primaries
Literature Review after 1986 by the author

Primary	Hand N=71		Foot N=54
SupraDiaphragmatic			
Bronchus	19 (26.7%)		15 (27.7%)
Breast	5		4
H&N	4		2
Thyroid	--		1
Parotid	1		--
Esophagus	6		2
InfraDiaphragmatic			
Uterus cervix	2	Endometrium	5
Stomach	2		--
Colon	6		7
Kidney	9		8
Ovaries	3		--
Urinary Bladder	3		2
Prostate	2		3
Choriocarcinoma	1		--
Other	3		3
No adequate data	5	unknown	2

Table 7.54 - Metastasis to the Hand
Metastatic Sites N= 55 (English literature)
Literature Review by Chung et al. 1983

Carpal bones	5.8%
Metacarpal bones	11.6
Proximal phalanx	26.1
Middle phalanx	13.0
Distal phalanx	36.2
Unspecified	7.3

Table 7. 55 - Metastases to the Foot
Metastatic Sites N=72
Literature Review by Zindrick et al. 1982

Tarsals	50%
Calcaneum	23%
Talus	8
Cuneiforme	7
Cuboid	5
Navicular	4
Unspecified	3
Metatarsals	23%
Phalanges	17
Unspecified	10

BONE METASTASES from an UNKNOWN PRIMARY

As already mentioned for the different localisations discussed, quite a number of skeletal metastases present in patients as a first sign of a previously unknown neoplasm (type 1 metastases).
From the reviews of these patients, the most common sites of first presentation and most frequently found primaries may offer some insight.

In the literature, all patients presenting with any metastases in any site are usually grouped together without a distinction between sites being made, making specific conclusions illusory. A patient with bone metastases from an unknown primary cannot be compared with a patient presenting with brain metastases from an unknown primary.
There are only a few series specifically addressing patients presenting with bone metastases first. We have grouped two series totalling 86 patients in order to try to derive some conclusions (table 7.56). The most frequently involved sites are the pelvis and the femur.

Table 7. 56 - Bone Metastases as First Presentation
Site of Metastases and Involved Primary (N=86)
Series of Simon et al.(1986) and Rougraff et al (1993)

Site	Involved Primaries
Skull (3)(°)	Kidney1, Unknown 2
Clavicle	Bronchus 1
Scapula (12)	Bronchus 7, Kidney 1, Liver 1, Unknown 3
Humerus (6)	Bronchus 2, Thyroid, Pancreas, Skin and Unknown each 1
Radius	Bronchus 1
Sternum	Bronchus 1, Ovary 1
Rib	Unknown 2
Spine (8)	Unknown 8
Pelvis(‘)(24)	Bronchus 11, Kidney 3, Liver 1, Breast1,Unknown 7
Femur (23)	Bronchus 9, Kidney 3, Prostate 2, Breast, Thyroid, Urin.Bladder, Colon 1 Unknown 9
Tibia-Fibula	Kidney 3, Unknown 1

(°) the number of cases.
(‘) including sacrum and ilium

Overall, the bronchus accounted for 38% and the kidney for 12.7%, while there were 29 or 34% patients where the primary remains occult. All spinal cases remained unknown. To the extent that the small number permits any conclusion, there is no site of predilection for any primary, except for the kidney in the lower extremity. Bronchial cancer is ‘everywhere’.

Table 7. 57 - Bone Metastases as First Presentation
Primary involved as found (N=115)
Data of Maillefert et al. 1993

	Women N=24		Men N=91
Unknown	54.2%		23.1%
Prostate	--		30.8
Bronchus	4.2		20.9
Kidney	16.7		8.8
Breast	16.7		--
Liver	4.2		6.6
Uterus	4.2	Other	10.0

Other studies have indicated a greater number of prostate cancers. Almost none of the studies distinguish between genders, rendering the results inconclusive. Only one report mentioned adequate gender-data (Maillefert et al.) (table 7.57). The primary

remained unknown in more than half of the female patients and in one third of the male patients. The low number of breast cancer patients is to be explained by the fact that the data are from a department of internal medicine.

Diagnosis

When metastases are found in a patient with an unknown primary, the academic reflex is to look for the site and type of the primary. During the last decades, the medical world has come to realise that such patients are Stage IV patients and have a rather low life-expectancy, so that diagnostic measures and treatment should be limited to the minimum.
Clinical examination may detect a breast, uterine, prostate and head and neck tumor. Blood analysis can give some indications, as with myeloma or prostate cancer, while a plain radiograph can detect obvious bronchial cancers. The data on table 7.56 (Simon et al.) may offer clues to the most probable primary.
When the metastasis is solitary, a biopsy, best with fine needle, can indicate the histology type. Open biopsy can of course be performed in cases of operative reduction of a inpending or pathological fracture (table 7.58).

Table 7. 58- Bone Metastases as First Presentation
Diagnostic Tests to detect Primary

Anamnesis, previous treatments, surgery?
Clinical Examination,
including gynecological and rectal
Tumor markers
Radiograph of thorax - Mammography
Bone scintigraphy
Fine Needle Biopsy or at surgery for fractures
Do not insist too much

The histology obtained can indicate renal cell, thyroid or liver cell cancer, but will usually yield only 'adeno-carcinoma' in more than 40%, epidermoid or poorly differentiated. This can alsodirect the exploration of a suspected organ. It is up to the clinician to decide on further exploration and palliative treatment depending on the state of the patient.

Nottebaert et al. have made some particular observations in the cases of bone metastases as first presentation:

1. there are significantly more spinal metastases cases with unknown primaries : 75% vs 27%;
2. there are significantly more spinal metastases with cord compression with known primaries: 45% vs 13%;
3. in their series, there were 55% cases with pathological fractures;
4. in the group presenting first with skeletal metastases, there were proportionally many more bronchial cancers than when the primary is already known : 41% vs 10% of all oncology patients.

In several clinical situations, a bone marrow aspirate is obtained. In rare cases, malignancy can be found, before the primary is known. In a series of 9000 aspirates, Wong et al. discovered 25 adult cases or 0.2%. The final diagnosis was as given in table 7.59.

Table 7. 59 - Bone Marrow Metastases
Found in patients with unknown primaries
Data of Wong et al.1993

Cytology		Primary	
Adenocarcinoma	17	Bronchus	7
Small cell	3	Prostate	2
Epidermoid	1	Stomach	1
Unclassifiable	4	Pancreas	1
		Rectum	1
		Bronchus (RX only)	6
		Inconclusive	7

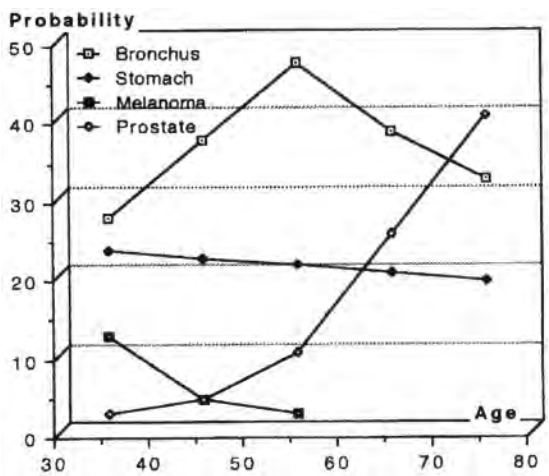


Fig.7.27 - Probability of the involved primary in cases of bone metastases in men depending on age (drawn from data of Basserman et al.)

Based on an autopsy study of 2,552 oncology-patients, Basserman et al. have mounted a probability scale of the primary that may be involved, depending on age and the metastatic sites. Although such data are not absolute, they are interesting as such, giving some idea of the repartition (fig.7.27 & 28).
A study of bone marrow cytology van detect metastases before any imaging. Its significance is now being progressively clarified, as it can exclude some patients from unnecessary treatments (Maguire et al.).

Myelophtisis or Leuko-Erythroblastic Anemia

Extensive bone marrow involvement by metastatic cells can overwhelm the overall function of the marrow and seriously impede red cell production, so that the marrow itself will try to compensate. In adult patients, yellow or inactive marrow will be reactivated, resulting in an extramedullary hematopoiesis. The products of the marrow will however be somewhat hastily formed, as nucleated red cells or erythro blasts will be thrown in the circulating blood, at first somewhat

difficult to distinguish from normal leukocytes.

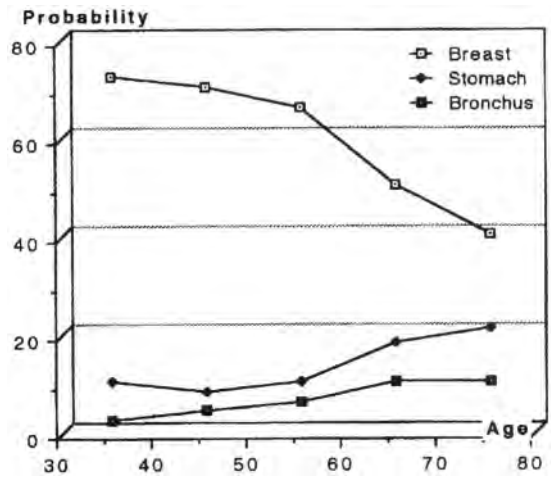


Fig.7.28 - Probability of the involved primary in case of bone metastases in women depending on age (drawn from data of Basserman et al.)

Table 7. 60 - Bone Marrow Extension and Distribution Classification by Munz

Type I: Normal bone marrow distribution with visualization of central and peripheral bone marrow, the latter confined to proximal one third or less in the femur.
Type II: Moderate bone marrow extension, beyond the proximal one third of the femur, but still confined to the femora and most proximal parts of the tibiae around the knee
Type III: Marked bone marrow extension, beyond the knee
Type IV: Central bone marrow is displaced to the periphery
Type V: non-visualization of any marrow, myelophtisis

The patient will be seen with anemia and a pseudo-hyperleukocytosis. In further evolution, true anemia will develop with inadequate compensation of the bone marrow activity or myelophtisis.
The function of the bone marrow can be evaluated with radionuclide (nanocolloids) scintigraphy. Based on the observed images, Munz has classified the stages of the bone marrow distribution (table 7.60). MRI is presently used, but this is better at indicating the bone marrow involvement than its hematopoietic function.

METASTASES to the REGIONAL LYMPH NODES

Metastases within the lymph nodes are well known and have been extensively studied. One can discern regional and non-regional node involvement. The first entails the involvement of regional lymph nodes tributary to every organ and will be discussed along with the spread of the different organ cancers in Part 2 of this book. The intensity of the involvement can be staged from none to extensive (N0-N3) by the UICC-TNM-code. Micro-metastases are detected mostly at immunohistochemistry and are by convention limited to a diameter of 2 mm and classified as pNla (Hermanek).

SENTINEL NODES

During the last decades, the concept of the sentinel nodes has been developed and applied in order to have a more appropriate approach to the problem of surgical dissection of the regional lymph nodes.
The sentinel node is the 'first' node to which lymph drains from a malignant lesion. Surgery involving removal of the sentinel node was first applied extensively for malignant melanoma, in order to circumvent the sometimes unusual draining of melanomas situated at the thoracal or abdominal skin sites.
The exploration and identification of the sentinel node is particularly particularly important for to malignancies outside the body cavities where the lymph nodes are readily accessible. The concept has been applied recently to breast cancer, but it is currently under development for many other cancers. Will experience in this area is, it is accumulating.
There is no doubt that the accurate identification of the 'first node where all the cancer cells go', is essential in order to avoid unneccesary dissection.

Diagnosis

While the metastatic nature of any lymph nodewill be obvious in patients with a known cancer, either at presentation or during follow-up, making a definite diagnosis when the primary is unknown is challenging. A good clinical examination, anamnesis and a panendoscopy of all head and neck regions is mandatory when the nodes are cervical and supraclavicular.

Fine needle aspiration cytology or even biopsy is the modern diagnostic measure of choice. The cytologic and histochemical characteristics are very helpful in directing the clinician to the suspected site. Nevertheless quite a lot will remain unknown, even at autopsy. Recently imaging methods with deoxy-Fluoro-F^{18}-glucose have been proposed to find the primary. Results are awaiting confirmation.

Pathways

It is well known that metastatic cells gain access to the lymph nodes via afferent lymphatics (fig.7.29). This is the predominant mode of spread. Some authors have pointed to the fact that metastatic cells were only found within the center of the node and not in the peripheral zones as could be expected from the route of the lymph within the node.
Examining the problem more thoroughly, Ivanov et al. were able to demonstrate at least in squamous cell

cancers, the cells could gain access to the lymph nodes via the postcapillary high-endothelial venules (Fig.7.30). These venules were described long ago and are restricted to the T-cell dependent paracortical and interfollicular areas of the node. They regulate the immunologic surveillance and the extravasation of lymphocyte subsets. These venous-mediated metastases could be called 'back-door' metastases (Ivanov et al.).

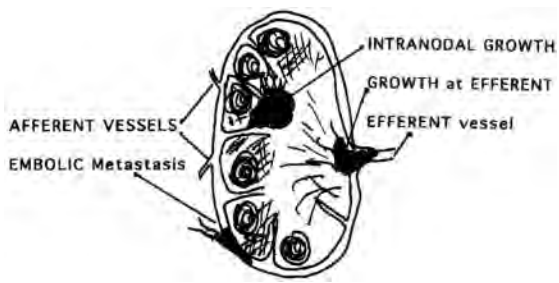


Fig.7.29 - Anatomy of the lymph node and some different kinds of involvement

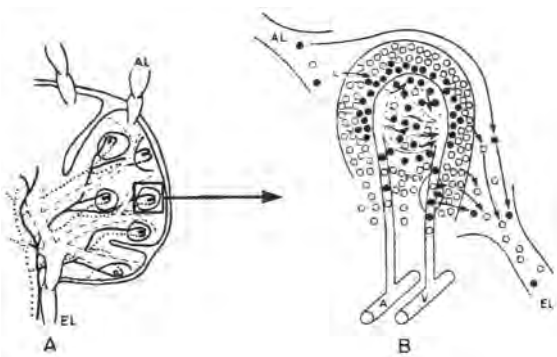


Fig. 7.30 - Vascularization of the lymph node. A. location of the germinal centers in relation to blood and lymphatic vessels; B. T and B-cells in and around the germinal center. (from Ivanov, with permission)

Pathology

Deciding wether to do the biopsy or fine needle aspiration cytology (FNAC), will depend on the size and the location of an abnormal node and the duration of the time that the node was present.
A lymph node size of 1.5x1.5cm should be the best discriminating size for malignant nodes and other causes. For inguinal nodes, a node larger than 1x1cm since one month should be biopsied (Habermann et al.).
Abnormal nodes can have several presentations, from tender, warm to fluctuant. They may be rubbery or hard, fixed or mobile, but no character is specific for malignancy. Metastatic cancer is mostly rock-hard, but malignant fast-growing nodes will present as tender nodes.

The efficiency of a biopsy may depend on the choice of the node excised from the different presenting in the nearby anatomical regions. Some tips have been given by Haberman et al. (table 7.61).

Table 7. 61 - Metastatic Lymph Nodes
Which to Biopsy ?
Recommendations of Haberman et al.

Peripheral nodes
1. The largest node in one region
2. The largest peripheral outside the inguinal zone
3. The best in the order of supraclavicular, cervical, axillary, inguinal

If no peripheral is present
1. Mediastinal nodes are easier to access than abdominal (retroperitoneal)

Try to avoid:
1. Parotid node: risk of nervus facialis
2. Cervical Posterior Triangle : risk of spinal accessory
3. Inguinal node: diagnostic rate only 53%

METASTASES to the 'NON-REGIONAL' LYMPH NODES

The UICC TNM code considers as N lymph nodes as long as they are 'regional', in the neighbourhood of the organ containing the tumor. A node beyond any involved 'regional' node is considered a distant metastasis.

A number of peripheral regions containing lymph nodes are within clinical reach, viz. the cervical and supraclavicular nodes, the axillary and the inguinal lymph nodes. All may be invaded by tumor cells coming from primary tumors at a certain distance (fig. 7.31).

The knowledge of this possibility is of importance in the evaluation of patients presenting with lymph nodes without symptoms of any primary.

Metastases to Cervical Nodes

The involvement of the cervical lymph nodes is well known for all the so-called Head and Neck tumors. We will not discuss the intricate relationship between the anatomical site of the primary.
Quite a number are well known presenting signs of an unknown primary.
They are rarely involved as distant metastases from infraclavicular cancers as breast, bronchial cancers and other.
There are hundreds of reports concerning diagnosis and management of cervical lymh nodes presenting from unknown primaries. Only a few have looked for the primaries although the results would appear to be rather disappointing, as between 20 to 80% are never

found. Anyhow, the follow-up is never reported as they can appear later or autopsy was not done. Furthermore, most series include the supraclavicular nodes, which are on an anatomical basis much more prone to be invaded from infraclavicular tumors (see further).

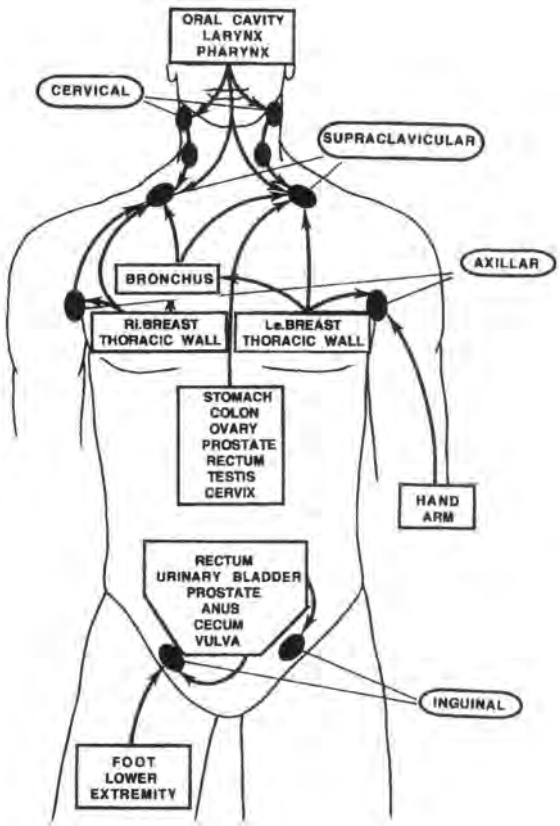


Fig.7.31 - Primary tumors that may metastasize in distant lymph node groups.

Molinari et al. have provided a statistical study relating the precise site of the cervical node to the site of the primary found (fig. 7.32). When the site in the neck is considered, some are much more frequently involved from definite primaries (table 7.62), though the correlation with the eventual primary was not included in the report. Other rare cases include cervical node metastases from neck paragangliomas and cerebral tumors (meningioma, glioblastoma).

Table 7. 62 - Cervical Nodes from Occult Primaries
Site in the neck involved
Literature review by Batsakis, 1981

Upper jugular (subdigastric)	71%
Mid-jugular (supra-omohyoid)	22
Submandibular	12
Spinal accessory	12
Submental	8
Supraclavicular	18

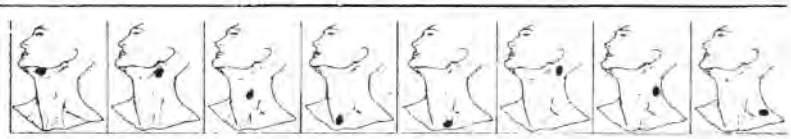
The involvement of the parotid nodes was discussed in Chapter 6.

Metastases to the Supraclavicular Nodes

Anatomy

The thoracic duct receives drainage from the right and left intercostal lymphatics and from the cisterna chyli. This latter receives lymph from lower right and left intercostal, gastric, superior and inferior mesenteric, right and left lumbar and right and left external and internal iliac lymphatics. At the cranial end, the duct receives lymph from the left jugular, left subclavian and left mediastinal lymph node vessels, and also from the left supraclavicular nodes (fig.7.32).

The thoracic duct terminates in the left subclavian vein, though some additional sites have been described. The right lymphatic duct receives lymph only from the right mediastinal, the right subclavian and jugular lymph vessels, but not from abdominal or



Floor of the Mouth	32,4	3,9	2,0	2,8	1,3			1,4
Tongue	22	8,6	2,9	2,1				1,5
Trig Retromolare	16,8	8,7	4,8	2,8		2,9		
Tonsil	10,6	10,1	4,4	0,8		9,6	8,7	10,3
Base of the Tongue	6,6	12,8	10,5	7,6	3,5	7,7	11,6	3,6
Larynx	3,2	9,3	12,8	13,1	3,9	4,6	1,5	7,6
Oropharynx	3,2		5,8	4,3		8,5	8,7	4,9
Nasopharynx	2,2	11,9	7,2	11,8		58,0	55,0	24,1
Palate	1,3		16,6	1,1				
Hypopharynx		14,9	20,7	25,1	4,2	7,7	11,6	24,8
Thyroid gland		8,9	11,3	26,7	22,8		2,9	16,5
Bronchus			0,4	1,3	40,0			2,5
GI-tract					12,3			1,4
Testis-Ovary					7,8			1,4
Other	1,7	10,9	0,6	0,5	4,2	1		

Fig. 7.32 - Composite diagram relating the site of the primary found in patients presenting with cervical metastatic nodes from unknown primary. Drawn from data on 131 patients, from Molinari et al.

pelvic vessels. It ends in the right subclavian vein. This explains why the left supraclavicular nodes are more frequently involved in infradiaphragmatic tumors (fig. 7.33).

The occurrence of metastatic lymph nodes in the supra-clavicular nodes can be explained by the anatomical ending in some cervical nodes, as the thoracic duct not always terminates straight into the subclavian vein (fig.7.34, Zorzetto et al.).

Data comparing both sides have been reported by Cervin et al. show almost no difference between left and right for the thoracic neoplasms, though left metastatic nodes are 5 times more frequent than at the right for abdominal and pelvic tumors. Palpation of the supraclavicular nodes is necesssary in the staging and during follow-up in patients with abdominal and pelvic tumors.

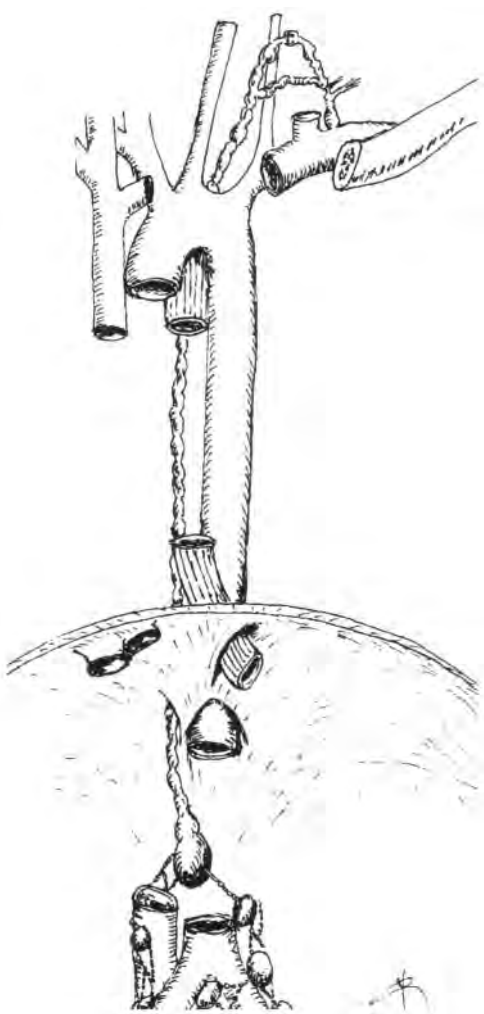


Fig.7.33 - The anatomy of the ductus lymphaticus.

During the progression of the lymphatic spread, supraclavicular nodes are invaded either from 'above' during the progression of head and neck and thyroid tumors, or from 'beneath' from the axillary region in breast cancer, or from cancers in the thoracal, abdominal and pelvic cavity. The Delphian node is a midline prelaryngeal lymph node, traditionally believed to be connected with a laryngeal or thyroidal tumor. It has not received much attention in the literature. It is located in the fascia over the thyroid isthmus and lies between the cricoid and thyroid cartilage.

The name Delphian has been given as it should have a predictive value, like the Delphian oracle (Olsen et al.)

The anterior left supraclavicular node is known as Virchow's node or as the signal node of Troisier, and will herald a malignancy from the thorax or abdomen, even pelvic.
These nodes can also be involved either from thoracal tumors or even from infradiaphragmatic neoplasms. The pathway of the latter is the ductus thoracicus.

Table 7.63 - Metastatic Supraclavicular Nodes
Comparative data between left and right sides
Data from Cervin et al.

	Left	Right
SupraDiaphragmatic Tumors		
Breast	7.3%	10.4%
Esophagus	2.1	1.0
Bronchus	16.7	14.6
Head and Neck	2.0	--
Total supradiaphragmatic	31.4	26.0
InfraDiaphragmatic Tumors		
Urinary Bladder	1.0%	1.0%
Cervix Uteri	9.4	1.0
Stomach	1.0	--
Colon	3.1	--
Prostate	3.1	1.0
Kidney	2.1	--
Testis	1.0	--
Unknown	4.2	2.1
Total infradiaphragmatic	24.9%	5.1%

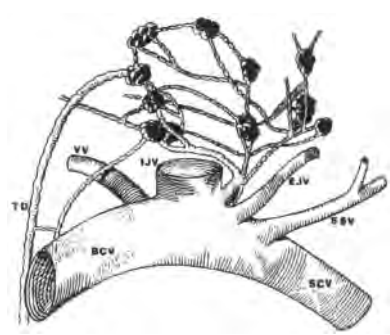


Fig.7.34 - Thoracic duct ending in lymph nodes of the cervical lymphatics and joining the subclavian vein (Zorzetto et al., with permission)

The supraclavicular node involvement from infraclavicular tumor has also been named the node of Virchow - Troisier.

Some decades ago, there was a tendency to make pre-treatment biopsies of these 'scalene nodes' as a staging method for ovary and cervical cancers. This practice has been abandoned, as positive nodes were found in a variable number of cases. Positive nodes were invariably found in stage III-IV patients with cancer of the ovaries or cervix uteri. Their presence had no impact on the treatment modalities.

Table 7.64- Cervical Nodes of Unknown Primary
Proportion of Infraclavicular Tumors involved
Survey of 9 selected adequately documented reports

	N	N infraclav.tumor
Skandalakis 1960	1061	131 (12.3%)
Greenberg 1966	35	8 (22.8%)
Fu et al. 1973	67	12 (18%)
Molinari 1977	139	89 (64.0%)
Adenis 1977	121	9 (7.4%)
Leipzig 1981	32	5 (15.6%)
Lee et al. 1986 (')		3-14%
Liu et al. 1997 (")	133	64 (48.2%)

(') literature review
(") diagnosis guided by fine needle cytology

A supraclavicular mass was mentioned as first recurrence in a patient with hepatocellular carcinoma, presenting later with an hemorrhagic brain metastasis (Lee et al.).

The number of infraclavicular tumors detected in patients with lower cervical nodes is proportionally not low. A survey of a number of articles containing adequate data are shown in the table 7.64.
It will be seen that in some series, the proportion of infraclavicular cancers found is quite high and must be ascribed to adequate diagnostic measures. With fine needle cytology (FNAC), Liu et al. found an infraclavicular cancer in nearly half of the patients.

Some interesting data are the incidence of supraclavicular nodes at autopsy in a number of common cancers (table 7.65).

Table 7. 65 - Supraclavicular Node Metastases
Incidence at autopsy
Modified from data cited by Batsakis 1981

	N	cases with SCN
Head Neck	67	28 (41.7%)
Thyroid	43	18 (41.8%)
Breast	395	318 (80.5%)
Bronchus	416	331 (79.5%)
Ovary	139	110 (84.0%)
Prostate	768	123 (16.0%)
Stomach	391	212 (54.2%)
Kidney	43	18 (41.8%)
Rectum Colon	584	93 (15.9%)

Recently, some interesting data were provided by Ellison et al. Of 309 FN-aspirates in 289 patients, metastasis were found in 55%, with 8% primary lymphoma. More importantly in 96 cases, it was the first evidence of an unknown primary. We have reorganized their data in table 7.66.
In 40% of the infradiaphragmatic tumors with supraclavi-cular metastases, it was a revealing metastasis, while for supradiaphragmatic cancers, the figure was 50%, though this is probably not significant.

Table 7.66 - Supraclavicular Node Metastases
Primaries in series of Ellison et al. (1999) (modified)

Primary	Known	Revealing	Total
Supradiaphragmatic			
Bronchus	8	25	33
Breast	25	4	29
Head Neck	0	3	3
Thyroid	0	3	3
Mediastinum	0	2	2
Total	33	37	70
Infradiaphragmatic			
Cervix Uteri	15	1	16
Stomach-Esoph	6	4	10
Ovary	5	4	9
Pancreas	1	7	8
Gallbladder	1	0	1
Testis	3	1	4
Colon	1	1	2
Kidney	1	1	2
Prostate	0	2	2
Urinary Bladder	0	2	2
Vulva	1	1	2
Sarcoma Extrem.	0	1	1
Total	34	25	59

Metastases to Axillary Nodes

The axillary nodes are mainly involved in breast cancer. Hundreds of reports have addressed this important relationship and this will not be discussed here. We can only remark that in several cases, in spite of suspicious mammography, no cancer was found at mastectomy. Many cases were reported as 'in situ', but one should remember that at autopsy of non-oncology patients, such findings are regular in patients of about 60-70 years of age.
Axillary nodes can harbor metastases from either carcinomas or melanomas of the skin of the upper extremity and of a large part of the trunk (fig.7.35).
They rarely have been encountered with Head and Neck cancers, but this also applies to bronchial and even ovarian cancers. In an autopsy study of thyroid cancer patients, Tollefsen et al. mention the occurrence of axillary nodes in 6 of the 70 patients, or about 10%.

Histology of the node will certainly differentiate first between lymphoma and carcinoma, either adenocarcinoma or epidermoid.
Reviewing some 'honest' series on axillary nodes where no mammary tumor was found, only a few authors have reported that in a relatively large number of patients, other distant cancers were found. Kemeny et al. mentions that 3 of the 4 men presenting with axillary nodes had a non-mammary cancer, without giving further details.

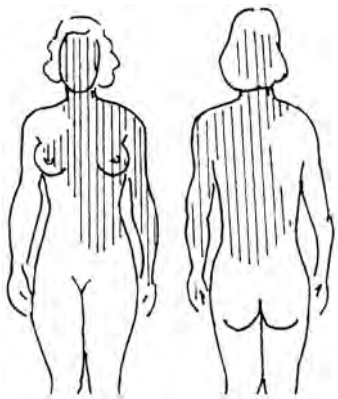


Fig.7.35 - The large skin surface draining to the axillary lymph nodes.

An overview of the rare reports is given in table 7.67. The gender was not always stated but the several cases of bronchial cancers were in men.
The lesson from these data is that when mammogram or pathology of the mamma is negative, one should look for a thoracal or abdominal problem!. Review of the patient files treated for 'occult' mammary lesions may well show interesting several years on.

Table 7. 67 - Metastatic Axillary Nodes
Patients presenting with Unknown Tumor
Summary of reports (')

Pharynx	1 case
Bronchial Cancer	5
Stomach	4
Pancreas	2
Colon	2
Urinary Bladder	1

(') reports of Feuerman et al 1962; Copeland et al. 1973; Hoerni 1973; Kemeny et al.1986

In recent years, a number of patients with ovarian carcinomas have been reported either as the presenting sign (one case!) or at follow-up. Some cases of pleural mesothelioma presenting with axillary nodes have been reported (see chapter 8).

After invasion of the abdominal or thoracal wall, the cells can take a pathway towards the axilla. We think nevertheless that hematogenous spread is also possible. As data on the reported patients are very limited in the reports, conclusions are difficult to draw.

Axillary lymph node involvement can occur via two mechanisms. Chest wall invasion allows malignant cells to travel to the axillary region and retrograde spread from the supraclavicular nodes is the second mechanism at least for ipsilateral nodes. Contralateral involvement is invariably associated with involvement of mediastinal or contralateral supraclavicular nodes (Marcantonio et al.).

Metastases to Retroperitoneal Nodes

The retroperitoneum is a common place for metastases within the lymph nodes from all pelvic cancers, but also from abdominal tumors, such as those of the colon, kidney and intestine.

Lymph nodes in the peri-aortic region are located around the aorta and the vena cava. Normal-sized non opacified para-aortic nodes may be seen routinely on CT-scans. Normally the outer contour of the aorta is easily seen in the lateral and dorsal aspect, while the vertebral column may partially obscure the dorsal outline. The anterior contour can be visualized on CT-scan to varying degrees, sometimes obscured by normal overlying anatomic structures or insufficient fat tissue. The loss of normal aortic contours, particularly in the lateral and dorsal areas, strongly suggests pathology in that region and will most commonly be a lymph node enlargement.
Large masses are either from testicular tumors or massive lymphomas.

Recent studies of the sentinel node in malignant melanoma have disclosed a direct pathway from the skin in the back at the loin towards the retroperitoneal nodes. It is claimed to occur in about 2.5% of the patients with a MM at the back (Uren et al.).

The involvement of this region is detailed further in the discussion of the different primaries in Part II.

A patient (M28) presented with a large mass in the retro-peritoneum, complicated with signs of acute pancreatitis. Several investigations were made without any specific diagnosis. Only at autopsy was a small nodule at the left testicle found to be a differentiated teratoma with embryonal carcinoma, similar to the retroperitoneal mass (Mössner et al.).

Uncommon metastatic tumor masses occurring in the region have been described. Caluori et al. described a large retroperitoneal mass presenting 2 years after surgery for a sigmoidal cancer. The mass was firmly adherent to the vertebral column with infiltration of the ureters and contained many bony structures such as heterotopic ossification. Most probably it was a secondary calcification due to necrosis of a conglomerate of metastatic lymph nodes.

A patient (F66) presented with a long-standing history of chronic abdominal pain radiating to the back. Eventually, a CT showed a mass consistent with an abdominal aortic aneurysm. A thyroid nodule was palpable but judged benign. Finally, a laparotomy disclosed retroperitoneal massive lymph nodes necessitating extensive vascular surgery. At histology anaplastic thyroid carcinoma was described, confirmed at autopsy(!), similar to the thyoid nodule (Lip et al.).

Metastases to the Inguinal Nodes

Metastatic inguinal nodes are common in cases of anal cancers, vaginal and vulvar and not uncommon in rectal, bladder, penile and prostatic cancers. A large part of the surface of the skin of the trunk and of the whole lower limb also drains to the inguinal nodes (fig. 7.36).

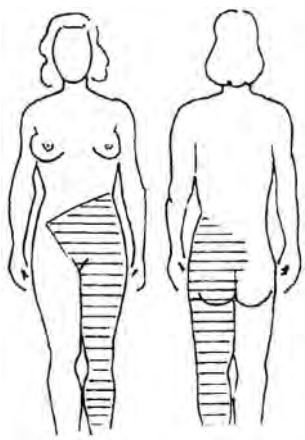


Fig. 7.36 - The skin surface draining to the inguinal lymph nodes.

The node of Cloquet, also known as Rosenmuller's node, is a deep inguinal lymph node near the femoral canal and distal of the inguinal fold.
Some case reports concerned ovarian cancers even a few as first presentation. During follow-up of gynecological tumors, the occurrence of inguinal nodes is not unusual.

A large one-institution statistics was published by Zaren et al. on 2,232 patients, who at diagnosis or during follow-up had inguinal nodes. In 22, the primary tumor was not found. Significant is that 50 different histologies were encountered. We tabulated the primaries in a more readable form than the original publication (table 7.68).
Malignant melanoma, penis and vulvar carcinoma are the most frequent primaries.

The lesson from this extensive study and the statistics is that inguinal nodes can occur in several unexpected situations, even from head and neck cancers.
The only other survey in the literature eis one small series involving gynecological tumors.
While the lymphatic pathway for pelvic tumors and those of the lower extremities is obvious, the pathway for head and neck tumors is not. We favor the hematogenous pathways, but the involvement of the abdominal wall is probably a strong factor in the spread from abdominal tumors.

Table 7.68 - Metastatic Inguinal Node Primaries found - Statistics in 2,232 patients (') Modified from data of Zaren et al.

Tumors commonly metastasizing to inguinal nodes	
Gynecological tumors	538 (24.1%)
Urology tumors	192 (8.6%)
Penis	82 (3.6%)
Skin lower extremity	395 (17.7%)
Soft tissue lower extremity	53 (2.3%
Rectum Anus	120 (5.4%)
This group	1380 (62%)
Tumors NOT metastasizing to inguinal nodes	
Trachea-Bronchi	48
Breast cancer	46
GIT (incl. pancreas,liver)	55
Kidney - Adrenal	25
Head and Neck (incl.eye, thyroid, salivary)	19
Skin of the trunk	130
Skin elsewhere	101
Various (eg. bone)	50
Unknown Primary	22

(') the site was not given for all patients !)

METASTASES to BENIGN and MALIGNANT TUMORS

The paradox of metastases in another primary is well documented in the literature. Some excised benign tumors have been shown to harbor cells from an unknown primary, leading to the diagnosis of a metastatic tumor.
Circulating tumor cells can be arrested anywhere in any capillary network, so that any other tumor with its own vascularity can also be clogged with cells from another tumor.
It is the pathologist who will and should make the diagnosis, as there will be no imaging or clinical sign of invasion of a tumor by tumor cells of another.
Anyhow this is a rare event. To the extent that data are available on such patients, only slightly more than 200 cases were published during the entire twentieth century. The majority involved benign tumors as receptors.
A genuine case of tumor to tumor metastases can only be accepted when the following criteria are fulfilled:

1. There must indeed be two different tumors, the donor being by definition a malignant one;
2. The recipient tumor must be a true neoplasm, either benign or malignant;
3. The metastasis must clearly be within the second tumor and not a contiguous invasion.

Of the 209 cases, metastases were found in 64 malignant tumors, the majority of them being kidney carcinoma (table 7.69). The different receptor-tumors found are listed in table 7.70. Metastasis of a malignant tumor was found in 145 patients. The large majority concerned meningioma.

Table 7. 69 - Metastases to Malignant Tumors
Distribution of Receptor Tumors (N=64)

Renal cell Cancer	26 (41%)
Brain Tumor	10 (16%)
Lymphoma - Leuk Nodes	7
Thyroid carcinoma	4
Pheochromocytoma	2
Prostate carcinoma	2
Ovary tumors	3
Stomach cancer	2
Testis, pancreas, parathyroid, sarcoma, pleural mesothelioma, rectum	1 each 1

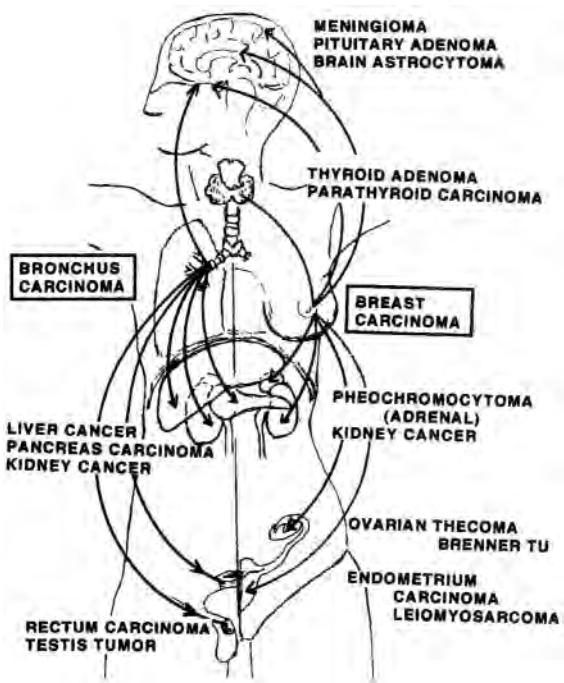


Fig. 7.37 - The most frequently reported 'receptor' malignant tumor sites in Bronchial cancer (left) and in Breast cancer (right).

As far as the primary metastasizing tumors are concerned, The predominance of breast and bronchial cancers is striking (table 7.71). In fig.7.37, we have grouped the most frequently reported malignant receptor sites for bronchial and breast cancer.

Table 7. 70 - Metastases to Benign Tumors
Distribution of Receptor Tumors (N=145)

Brain benign tumors (hemangioblast, schwannoma, a.o.)	11
Parathyroid adenoma	4
Thyroid adenoma	4
Meningioma	72 (50%)
Pituitary adenoma	15 (10%)
Ovarian (thecoma, Brenner, fibroma)	5
Uterine leiomyoma	31 (21%)
Various	3

About 19 of the primary tumors, as far as we could judge from the reports we were able to collect, were found because of the pathology description of the recipient tumor. In 8 of them, a bronchial cancer was discovered, a cancer well known for its type 1 presentation (table 7.72). Of the 19 cases, seven meningiomas led to the diagnosis of a primary.

Table 7. 71 - Metastases to Tumors
Distribution of the Donor Tumors

	in Benign N=145	in Malignant N=64
Breast	69 (47.5%)	14 (22%)
Bronchus	29	19 (30%)
Carcinoid	4	1
Cervix Uteri	2	1
Galbladder	2	1
Kidney	8	4
Melanoma	3	3
Prostate	5	6
Stomach	3	3
Thyroid	--	3
H&N cancers	--	3
Unknown adenoca	3	--
Others	17	8

Table 7. 72 - Tumor to Tumor Metastases
Type 1 presentations (N=19)

Donor		Recipient	
Bronchus cancer	8 cases	Meningioma	7 cases
Breast cancer	4	Kidney	1
Unknown Adeno	2	Uterus Leiomyo	3
Kidney	2	Brain	2
Carcinoid, colon, pancreas each 1			

METASTASES to TRANSPLANT RECIPIENTS

Transplant recipients develop oncology problems in three ways:

1. a malignancy of any organ of the recipient him or herself, either de novo or as a recurrence from a previously treated one;
2. a malignancy due to the immunosuppressive medication administrated in relation to the transplantation;
3. growth of malignant cells inadvertantly transplanted with the homograft from the donor.

Since it falls within the book's subject, we will only discuss the third possibility.
Reviewing the literature in 1978, Peters et al. found reports on malignant tumors transplanted with the renal homograft including bronchogenic carcinoma, breast cancer, thyroid carcinoma, hepatocellular carcinoma, cancer of the sinus pyriformis and choriocarcinoma.

Table 7.73 - Reported Cases of Cancer Transplant with Homografts from Donor to Recipient

Author	Donor	Cancer	Homograft	Recipient	Cancer
Gokel 1977	F30	Choriocarcinoma(°)	Kidney	M47	1 mo choriocarcinoma
Peters 1978	M42	Spleen -Melanoma(')	Kidney	M49	widespread melanoma
Lefrancois 1987	??	Medulloblastoma	Kidney - Pancreas??		4 mo kidney metastases
		(surgery + shunt)	Kidney	??	later kidney metastases
			Heart	??	Liver and Bone marrow
Marsh 1987					
Baquero 1988	F36	Choriocarcinoma	Liver	F20	Widespread choriocarcinoma
			Kidney	F??	Widespread choriocarcinoma
			Kidney	F??	Cured choriocarcinoma
			Heart	M46	No problems in first 10 mo
Leifer 1989		Glioblastoma	Liver		
Morse 1990			Liver		
Ruiz 1993	M42	Glioblastoma	Kidney	F46	17 mo kidney metastases
		(no shunt)	Kidney	M23	18 mo kidney metastases
ValBenal 1993	same case as Ruiz et al.				
Colquhoun 1994	M32	Glioblastoma	Kidney	M32	10 mo subcutan. et kidney
		(no shunt)	Kidney	F23	10 mo kidney metastases
Jonas 1996	F48	Glioblastoma	Liver	F28	Liver metastases
		(no shunt)			
Kunish Hoppe 1998	??	Renal cell cancer(')	Kidney	F50	Renal cancer + pelvic node

(°) the transplant team was unaware of the diagnosis of cancer in the donor
(') problems in the recipient lead to the diagnosis in the donor

Other cases have included myeloma and malignant melanoma. Since the early period of transplants, awareness of these accidental tumors has lead to much greater selectivity in selecting the donor kidney. Homograft transplants from cancer patients are now excluded, except from patients with skin cancers and with primary brain tumors, in view of the very low incidence of distant metastases.

As we will discuss in chapter 12, brain tumor patients who heve had surgery and ventricular shunts in particular, have been considered to have be somewhat more prone to develop distant metastases. This has also led to the elimination of these patients for homograft procurement. Nevertheless, a number of patients have been reported with distant metastases who have not had any skull surgery.

We retrieved ten cases of a cancer transplant in a recipient (table 7.73). Choriocarcinomas have been transplanted in the absence of knowledge about previous treatments. The melanoma and renal cancer cases were diagnosed after problems in the recipients, but in at least three cases of glioblastoma only classic surgery but no shunt had been performed.
In view of the very low risk, saving the life of the recipient who has been waiting for a long time and whose short term pathology is grim will take precedence over caution.

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Caution: References are given for documentary purposes. Not all have been reviewed or used to the redaction of the text. We do not claim completeness of data. The references are as much as possible grouped per subject heading.

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Metastases to Homograft Recipients

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THE ANATOMY AND CLINICS of METASTATIC CANCER

PART II THE PRIMARY AND ITS METASTASES

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8

METASTASES from THORACIC TUMORS

Cancer of the Bronchus
Cancer of the Pleura - Mesothelioma
Cancer of theThymus - Thymoma
Malignant Tumors of the Heart
Cancer of the Male Breast
Cancer of the Female Breast

METASTASES from BRONCHOGENIC CARCINOMA

Common Metastatic Pattern

The pattern of hematogenous metastases has been studied exclusively at the hand of autopsy series. However, these series may differ in several important aspects. They may include untreated, operated and/or irradiated patients. The pattern of metastases in such patients is possibly influenced by the treatment, but data are scarce and difficult to analyze. Another major problem is the absence of a standardized autopsy protocol, and the subsequent histological examination. Metastases can be macroscopic or only microscopically confirmed.
In our review of the literature, we could find influence of the following factors on the pattern: age, gender, histology type, interval between resection and death and the extent of mediastinal nodal involvement.
Although the dual step has found widespread acceptance, since tumors (esp.bronchial ones) have ready access to pulmonary and other veins, their cellsare able to disseminate via the blood right from an early stage of the tumor's evolution (Onuigbo).

Table 8.1- Bronchogenic Carcinoma
General pattern of metastases
Literature data (autopsy series)

Site	Gabler 1959 N=51	Barz 1982 N=935	Oehler 1983 N=649	Brunger 1984 N=426
Group1				
Liver	58%	22%	33%	40%
Adrenal	56	14	24	34
Bone marrow	55	19	23	29
Group2				
Kidney	33	9	17	14
Thyroid	28	5	4	6
Brain	22	12	16	18
Group3				
GIT	11	--	3	--
Spleen	10	2	1	--
Heart	2	1.2	--	--
Muscle	4	--	--	--
Skin	7	--	4	--
Pancreas	--	3.5	6	5.2

Overall Pattern

It would seem that distant metastases from bronchial carcinoma can be divided into three (or four) groups (Gabler et al.). The first group concerns organs with the highest incidence such as liver, adrenals and bone (marrow), the second has intermediate incidence as kidney, brain and thyroid, while the third group includes organs with a low incidence, i.e. gastrointestinal tract, spleen, heart, muscles and skin. A fourth group includes rare sites of metastases and those labeled as unusual (table 8.1).
Barz et al. have identified a particular group of patients; those with only one or solitary metastases at autopsy. The high incidence of brain metastases is a particularity of this group (Table 8.2).

Table 8.2 - Bronchogenic Carcinoma
Metastatic site when only 1 metastases is present
Data of Barz et al. N=299

Brain	23.1%	Thyroid	0.7
Bone	20.4	Pancreas	1.0
Liver	20.1	Spleen	0.7
Kidney	6.7		

There is apparently an interdependance between some metastatic sites when only 2 metastases are present. Liver metastases are more frequent when bone metastases are also present and vice-versa, but also with adrenal metastases, all of which belong to the first group. But the sites of the second group are also more frequently involved when those of the first group are(Table 8.3).

Table 8.3- Bronchogenic Carcinoma
Interdependence of metastatic sites
for patients with two metastases (N=267)
Modified from Autopsy data of Barz

	second site considered					
	Li	Bo	Ad	Br	Ki	Th
Liver	+	49%	18%	21.4%	8.7%	6.0
Bone	48	+	25	18	7.6	5.3
Adrenal	24	22	+	9	3.8	2.6
Brain	18	16	9	+	3.8	2.6
Kidney	6	6	3	2.6	+	0.7
Thyroid	4	4	2	2	1	+

This correlation is fully understandable according to

the 'favorable soil' theory of Paget. When two different organs are both good 'recipients', both are sure to have a higher incidence than other organs.

Influence of Age

Data from a refister, specifically for bronchial cancer, showed for the number of metastases at time of diagnosis a significantly negative correlation with increasing age. While more than 80% of the patients youn-ger than 40 yrs will have metastases, only 50% of those aged over 70yrs will have. The patients were not stratified according to type of metastases, histology or any other feature (Ershler et al.) (fig.8.1).

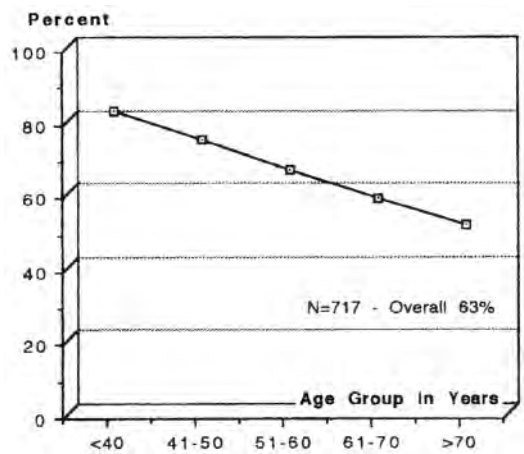

Fig 8.1 - Bronchogenic Carcinoma - Relationship between age and presence of metastases at diagnosis. N=717 (1983) overall incidence is 63% (Redrawn from Ershler et al.)

Influence of Interval between Resection and Death

In a series of 125 patients who died after resection, a progressive increase in the number of metastases was found with time. This can be explained by the progressive growth of the 'invisible' metastases already present at surgery (Table 8.4).

Table 8.4 - Bronchogenic Carcinoma
Relationship between time after surgery and number of metastases. Data of Weiss et al.

Time	No Residual disease at death		All patients	
< 30 days	11/35	31%	16/44	36%
1-5 mos	9/18	50	18/27	67
6-11 mos	11/14	79	17/20	85
>12 mos	13/16	81	28/34	82
All	44/83	53	79/125	63

If such series had been reporte 'in toto' the proportion of metastases would have been lower, but when the interval is taken in account, other data are obtained.

Influence of Tumor size

The size of the primary tumor has an important influence on the incidence of metastases, but how does it correlate? Is it only a parallel increase of the several tumors or is it generated by the growth of the primary?

The data reported by Kunz et al. concern a series of 170 patients of whom no less than 94 were only diagnosed at autopsy. A linear increase in the amount was noted with size, but also the appearance of more 'other' sites. Above 6 cm, the incidence almost doubles (Table 8.5).

Table 8.5 - Bronchogenic Carcinoma
Relationship between size of primary and number of metastases
Data of Kunz et al.

	Tumor Size - 2.9 cm	3-5.9 cm	>6 cm
Site	N=48	N=45	N=53
Lung(')	46%	58%	70%
Bone	38	42	55
Liver	31	44	58
Adrenals	21	24	45
Brain	19	27	38
Heart	13	13	28
Kidney	10	20	23
Other	N=14(°) (29%)	N=13 28%	N=29 54%

(') it is not clear if this concerns heterolateral lung
(°) this means that 14 other metastases were found

The sites of the bone metastases were examined separately and they correlated also with the size of the primary. The data are interesting as they are rarely reported in the literature (table 8.6). Their data permit calculation of the number of metastatic 'events' per patient. The figure increases with the size of the primary.

Table 8.6- Bronchogenic Carcinoma
Size of primary and site of Bone Metastases
Data of Kunz et al.

Site	Tumor Size - 2.9 cm N=18	3-5.9 cm N=19	>6 cm N=29
Lumbar C.	61%	63%	93%
Thoracal	56	68	90
Cervical	28	37	45
Ribs	N=3	26	41
Skull	N=2	N=2	17
Pelvis	N=2	N=2	14
Other	N=2	N=1	N=6
Total events	37	42	93
Event/patient	2.0	2.21	3.2 (')

(') calculated by the author.

Influence of Regional Nodal Involvement

A similar trend was observed for the influence of the

nodal involvement on the number of hematogenous metastases and on the number of metastatic sites.
The number of sites increases with the extension of lymh node involvement.

Table 8.7- Bronchogenic Carcinoma
Relationship between regional nodal involvement and number of metastases from data of Kunz et al.

Site	N0 N=28	Only thor. nodes N=72	Thorac. & Abdom.Node N=46
Bone (')	25%	32%	57%
Brain	21	32	26
Liver	14	42	70
Adrenal	N=2	32	43
Heart	N=3	14	30
Kidney	N=2	15	28
Other	N=0	N=22	N=36
Total M	N=24	N=144	N=153
M/pat (°)	0.8	2.0	3.3

(') data of 'lung' are omitted for the reason mentioned
(°) calculated by the author

Table 8.8- Bronchogenic Carcinoma
Site of metastases according to histology
Data of Brunger et al., N= 426 1984

Site	Histology type Epiderm.	Adenoca	Large	Small
Liver	23.8%	**43.1%**	23.2%	**57.7%**
Adrenal	35.7	**44.8**	27.9	**42.3**
Bone	20.2	24.3	23.2	**35.4**
Kidney	13.1	15.5	7.0	**20.1**
Brain	14.3	**20.7**	14.0	**19.6**

Table 8.9 - Bronchogenic Carcinoma
Site of metastases according to histology
Data of Barz et al., N=198

Site	Histology type Epiderm. Anepi	Epi	Adenoca	Large	Small
Liver	34.4	16.7	26.8	38.1	**59.7**
Adrenal	27.6	13.0	22.2	30.7	**31.0**
Bone	27.6	14.4	41.2	36.6	**46.5**
Kidney	**20.6**	**17.2**	11.0	14.9	13.7
Brain	27.3	8.8	23.5	21.8	**27.0**
Pancreas	3.1	1.4	0.7	5.9	**13.7**

Table 8.10 - Bronchogenic Carcinoma
Site of metastases according to histology
Data of Kunze et al. N=416 1985

Site	Histology type Epiderm.	Adenoca	Large	Small
Liver	31%	35%	38%	**62%**
Adrenal	23	32	31	**35**
Bone	38	42	19	**58**
Kidney	**23**	<1%	<1%	22
Brain	18	19	25	**35**
Pancreas	<1%	<1%	<1%	**13**

Influence of Histology

A number of studies have reported data, virtually all from autopsy data. In order to compare them properly, we have regrouped them all the same way. The highest frequency is noted for small cell carcinomas, and the lowest for large cell tumors (Table 8.10).
All these data confirm the well-known high propensity of small cell carcinoma for hematogenous metastases.

Data specific fto Adenocarcinoma

Stenbygaard et al. have extensively studied bronchial adenocarcinomas. Data have been reported for stage I-II patients as well as at autopsy. Advanced cases were found to have much more liver, adrenal, pericardial and skin metastases (Table 8.11), as would be expected.

Table 8.11- Bronchial Adenocarcinoma
Site and incidence of distant metastases
Autopsy-data of Stenbygaard et al.

	Operated I-II N=35	Inoperable, treated with chemotherapy N=184 at autopsy
Liver	37.1%	54%
Adrenal	17.1	43
Bone	20.6	41
Kidney	17.1	18
Thyroid	none	6
Brain	33.3	41
Spleen	8.6	9
Heart	5.7	6
Pericard	8.6	23
Skin	3.0	23
Pancreas	none	3

Considered by some authors as a variety of adenocarcinoma, bronchio-alveolar carcinoma has been identified and may be assumed to account for about 10% of the adenocarcinomas. Data on metastatic spread are only available from a study of Feldman et al. based on 25 patients. They had significantly more intra-pulmonary metastases due to the well-known tenedency for metastases to occur with 'lepidic growth' in the lungs. They had also significantly less pleural and mediastinal node metastases, but for all other sites no difference was observed.

Data specific for Small-Cell Carcinoma

We found two reports detailing hematogenous metastases sufficiently well to allow some analysis. The series of Elliott et al. concerns patients treated only with chemotherapy (non-resected), whereas the series of Jereczek et al. includes patient who have had chemotherapy, radiotherapy or only palliative treatment. They are virtually identical to the above-mentioned data.

As can be expected, the number of metastases increases with stage, from limited to extended disease. Both series are similar, though the low number of bone and brain metastases seems improbable. Treatment had no effect except when surgery was radical. Neither radiotherapy nor chemotherapy had any influence (Elliott et al.).

Table 8.12- Small cell Bronchogenic Carcinoma
Hematogenous metastases

	Elliott LD	Elliott ED(')	Jereczek N=174(°)
Liver	37.6%	73.5%	49.0%
Adrenal	31.6	26.0	25.0
Bone	30.9	56.2	7.0
Kidney	8.0	16.0	18.0
Brain	32.4	37.3	17.0
Pancreas	13.6	17.4	12.0
Meninges	5.2	10.2	no data
Thyroid	5.0	4.6	6.0
Spleen	<1	3.0	no data
Pericardium	no data		11.0

(') LD: limited disease, ED: extensive disease
(°) 3 patients had no metastases

MEDIASTINAL LYMPH NODES (Regional)

Mediastinal lymph nodes must be considered either from the point of view of the TNM classification or from an anatomical point of view.

TNM-classification

In the TNM classification the lymph nodes are divided according to the degree of invasion by the tumor (table8. 13)

Table 8.13- Bronchogenic Carcinoma
International N-stage

Nx : Regional lymph node cannot be assessed
N0 : No regional lymph node metastasis
N1 : Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes involved by direct extension of the primary tumor.
N2 : Metastasis to the ipsilateral mediastinal and/or subcarinal lymph nodes.
N3 : Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph nodes.

Table 8.14- Bronchogenic Carcinoma
Quick reference chart for N
Modified from Lababede et al.

	N1	N2	N3
Peribronchial (ipsilat)	+	o	o
Hilar ipsilateral	+	o	o
Hilar contralat.	o	o	+
Subcarinal	o	+	-
Mediast.ipsilat.	o	+	-
Mediast.contralat.	o	o	+
Scalene	o	o	+
Supraclavicular	o	o	+

In other words, hilar nodes are N1 and mediastinal nodes are N2.

Table 8.14 (modified from Labadede et al.) provides an easier way to establish the code.

Lymph node mapping

Naruke was the first to delineate the sites of lymph nodes. Single digits (1-9) were assigned to the mediastinal (N2)-nodes while double digits (10-13) were assigned to the intrapulmonary nodes. According to this system the hilar nodes are nr.10 and are the proximal lobar nodes immediately distal to the visceral pleural reflection. As such, it has been proposed to discard the name of hilar nodes, confiding with the TNM classification.

This system was later adopted by the American Thoracic Society (ATS), but 10 is divided into 10L and 10R (left and right) and 4 includes the azygos nodes.

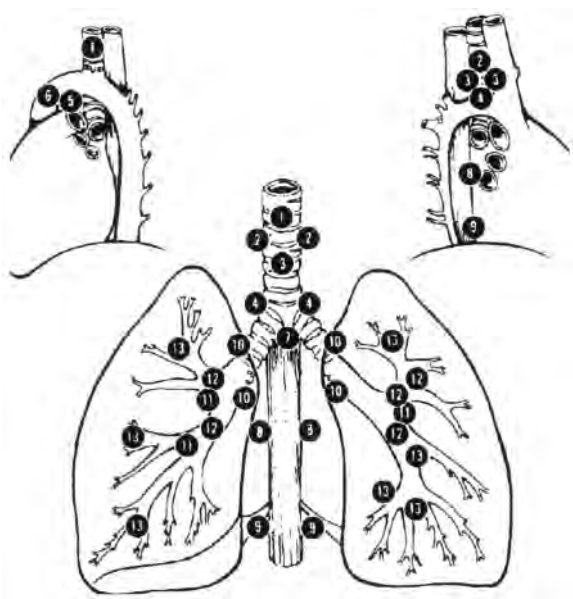

Fig. 8.2 - Bronchogenic carcinoma - Lymph node stations nomenclature recommended by Naruka and later adopted by the American Joint Committee on Cancer

Legend:

N1 nodes 10: hilar, 11: interlobar, 12: lobar; 13 segmental and 14 subsegmental.

N2-nodes 1: highest mediastinal, 2: upper paratracheal, 3: pre-and retrotracheal, 4: lower paratracheal (includes azygos nodes), 5; subaortic(aortic window), 6: paraaortic (ascending aorta or phrenic), 7: subcarinal, 8: para-esophageal (below carina) and 9: at pulmonary ligament.

We have only found data in the report by Kunze et al. (Table 8.15). In spite of the recommendations to use the coded numbers for each lymph node site, they are almost never used in such reports.

A Note on Imaging

There is extensive literature on imaging and detection of mediastinal and distant metastases. We will not discuss it further, though it is worth mentioning that the recent advent of FDG-PET scan has led to new developments. This method is presently the non-invasive method of choice in nodal staging. Several authors, reviewed by Klemenz et al. have outlined its high negative predictive value, substantially reducing the need for invasive mediastinal surgical staging in NSCLC. A negative PET makes medisatinoscopy unnecessary.

Furthermore the same study can at the same time perform a whole-body imaging to detect distant metastases. It should provide more accurate thoracic and extra-thoracic staging of NSCLC than conventional imaging methods. It is extremely useful in unclear CT and/or MRI-studies and particularly accurate for bone involvement (Klemenz et al., Van Steenkiste et al.).

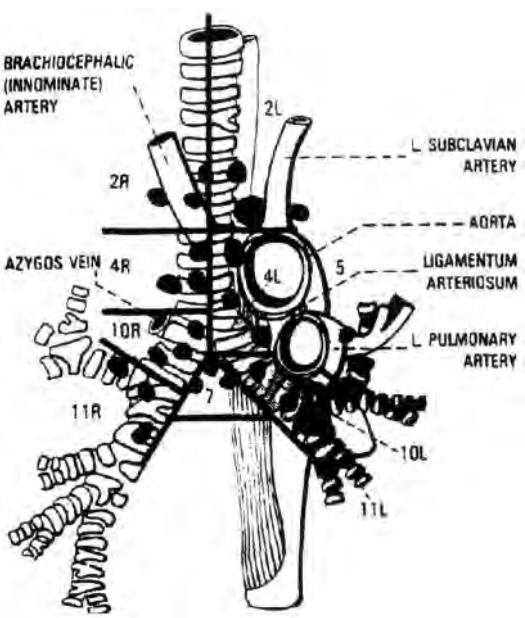

Fig.8.3 - Bronchogenic carcinoma - Lymph node station groups recommended by the American Thoracic Society

Table 8.15 - Bronchogenic Carcinoma
Involvement of lymph node stations
by histology type (autopsy series)
Data of Kunz et al. 1985

Site	Histology type Epiderm. N=33	Adenoca N=26	Large N=15	Small N=59
hilar(N1)	59%	69%	60%	78%
mediast	42	38	33	49
abdom.	15	19	27	27
cervic.	15	(1)	(3)	8
supracl.	18	(2)	(2)	(2)
axillar	(1)	(1)	(1)	(1)
inguin.	(1)	(1)	(1)	(1)

() within parentheses number of cases.

Table 8.16 - Bronchogenic Carcinoma
Definitions of Lymph Node Stations
(American Thoracic Society)

2R : Right upper peritracheal nodes: nodes to the right of the midline of the trachea between the intersection of the caudal margin of the innominate artery with the trachea and the apex of the lung (includes highest R mediastinal node).

2L: Left upper peritracheal (supra-aortic) nodes: nodes to the left of the midline of the trachea between the top of the aortic arch and the apex of the lung (includes highest L mediastinal node).

3 . Prevascular and retrotracheal nodes: may be designated 3A (anterior) and 3P (posterior): midline nodes are considered ipsilateral.

4R: Right lower peritracheal nodes: nodes to the right of the midline of the trachea between the cephalic border of the azygos vein and the intersection of the caudal margin of the brachiocephalic artery with the right side of the trachea (includes some pretracheal and paracaval nodes).

4L: Left lower peritracheal nodes: nodes to the left of the midline of the trachea between the top of the aortic arch and the level of the carina, medial to the ligamen-tum arteriosum (includes some pretracheal nodes).

5 : Aortopulmonary nodes: subaortic and paraaortic nodes, lateral to the ligamentum arteriosum or the aorta or left pulmonary artery (LPA), proximal to the first branch of the LPA.

6 : Anterior mediastinal nodes: nodes anterior to the ascending aorta or the innominate artery (includes some pretracheal and preaortic nodes).

7 : Subcarinal nodes: nodes arising caudal to the carina of the trachea but not associated with the lower lobe bronchi or arteries within the lung.

8 : Para-esophageal nodes: dorsal to the posterior wall of the trachea and to the left and the right of the midline of the esophagus.

9 : Right or left pulmonary ligament nodes: nodes within the right or left pulmonary ligament.

10R: Right tracheobronchial nodes: nodes to the right of the midline of the trachea from the level of the cephalic border of the azygos vein to the origin of the right upper lobe bronchus.

10L: Left peribronchial nodes: nodes to the left of the midline of the trachea between the carina and the left upper lobe bronchus, medial to the ligamentum arteriosum

11 : Intrapulmonary nodes: nodes removed in the right or left lung specimen plus those distal to the main stem bronchi or secondary carina (includes interlobar, lobar and segmental nodes). Post-thoracotomy staging may designate
- 11 interlobar
- 12 lobar
- 13 segmental
- 14 subsegmental

These data are only indicative, but should be related to the site within the tree and possibly also to the type of treatment, although this has been shown to be of importance in a few reports to be of any importance. Note however the importance of abdominal nodes,

probably retroperitoneal nodes, amounting to between 15 and 30% of the patients. Blockage of the mediastinal lymph channels is probably the cause of a reflux towards the abdominal nodes. Further abdominal spread may follow .The distribution of involved nodes depends heavily on the location of the primary within the tracheo-bronchial tree. The frequency may also depend on its histology. Clinical series are, however, not suitable to study this, as they include selected patients at best without N2-patients, who are in fact not curatively treated. As such, autopsy series, arranged according to histology, are preferable, although rarely reported according to the histology type.

Lymph Node Mapping in surgical cases

Only a few reports provide adequate data. From 544 surgical cases, Kayser et al. described the number of resected and involved lymph nodes according to the lymph node mapping (Table 8.17).

Table 8. 17- Bronchogenic Carcinoma
Number of resected and involved lymph nodes
Surgical cases, all histologies N=544
Data of Kayzer et al. 1990

Site	N resected nodes		N involved nodes	
1/2	311	57%(')	41/311	13%
3	379	**70**	38/379	10%
4	183	34	24	13
5	272	50	42	15
6	286	53	52	**18**
7	162	30	31	**19**
8	205	38	11	5
9	174	32	16	9
10	282	52	50	**18**
Total	2254	100	305/2254: 13.5%	

(') percent of the 2,254 resected nodes

Table 8.18 - Bronchogenic Carcinoma
Number of resected and involved lymph nodes
Modified from Watanabe et al. 1990

	RUL		RM/LL		LUL		LLL	
	Pat	No	Pat	No	Pat	No	Pat	No
Ly St.	45	**88**	36	74	35	67	8	12
1	4		1		--		--	
2	18	20.4%	11	15	1		--	
3	29	**33%**	17	23	10	15%	--	
4	16	18	1	13	6	9	1	
5	--		--		25	**37**	1	
6	--		--		15	22	2	
7	16	25	18	**34%**	7	10	3	(37%)
8	4		4		1		4	(50%)
9	1		2		2		1	
total	88meta		74		67		12	
m	1.96/pat		2.06/pat		1.88/pat.			

RUL: right upper lobe; RMLL: right middle lower lobe; LUL: left upper lobe; LLL: left lower lobe; LySt.: lymph station; pat: number of patients; no: percentage of positive nodes resected for this site.

In general, 13.5% of the resected nodes are involved when surgery is performed (in operable cases). The amount involved is the highest in stations 6 and 7, but this depends on the localization of the primary, and to a certain extent on the histology type. When central tumors are compared with peripheral tumors, the central tumors only will have double the frequency of lymph nodes at 3, while the incidence in the other sites will not be different (data not shown) (Kayzer et al.).

The site of the primary within the tracheobronchial tree has some influence on the degree of involvement in the different stations. Watanabe et al. reported on 124 patients operated for N2 tumors and provided the data on table 8.7.

Table 8.18 indicates that the site with the highest number of involved nodes clearly depends on the anatomical location of the primary. Station 3 will be the most frequently involved for the right upper lobe tumors, 7 for lower right and site 5 for left upper lobe.

In their review of the pre-therapy CT scans of 266 non-small bronchial cancer patients, Kiricuta et al. accurately mapped the different nodes involved according to the side of the primary. The incidence of involved contralateral nodes is always clearly less than the ipsilateral, while the subcarinal are involved at the same rate no matter what side the primary is on (fig.8.4).

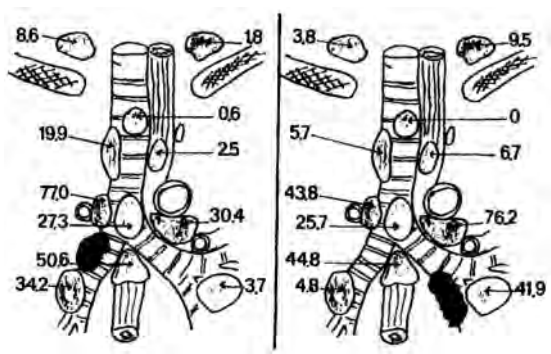

Fig.8.4 - Incidence of involvement of the regional lymph nodes for right-sided (N=161) and left sided (N=105) NS bronchial cancer. Redrawn from data of Kiricuta et al.

Other interesting data were reported by Oda et al. for 524 operated clinically stage I patients. The nodes involved also depend on the size of the primary and its histology (Table 8.19).

Table 8. 19- Bronchogenic Carcinoma
Number of resected and involved lymph nodes
Operated clinically stage I -patients
Data modified from Oda et al. 1998

	Squamous cell			Adenocarcinoma		
Size	Number	N1	N2	Number	N1	N2
-10 mm	12	none	none	9	none	none
11-20	27	7.4%	none	106	8.5%	11.3
21-30	47	6.4	4.3	122	7.4	11.5
31-	38	13.7	3.7	96	10.4	26.0
Total	154	8.4	**6.5**	333	8. 0	**15.3**

The number of N2 metastases for clinically stage-I is

twice as high for adenocarcinoma as for squamous cell tumors. However, the resulting pathological stage should also have been reported for these resected tumors.

Non-Regional LYMPH NODES

Lymph nodes outside the thoracic cavity can be involved by bronchial carcinoma (table 8.20).
The node clinically most frequent involved is the supra-clavicular/cervical node (N3), but axillary nodes have been reported in up to 5% of the autopsy cases.
Data from a large multi-institutional trial enrolling 1,370 patients with small-cell bronchus cancer, disclosed an incidence of 17% for supraclavicular nodes. Forty-four percent were in the limited disease group.
Axillary lymph nodes were found in less than 1% of the 1,486 patients submitted to surgery (Riquet et al.). Inguinal nodes have also been reported (fig.8.6).

Table 8. 20- Bronchogenic Carcinoma
Extra-thoracal Lymph nodes involved

	Martini (Autopsy)	Riquet (Surg.N=1486)
Abdominal	20.7%	3/22
Cervical	17.4	7/22
Supraclavicular	4.2	2
Retroperitoneal	8.1	---
Axillary	6.6	9
Peripancreatic	6.5	---

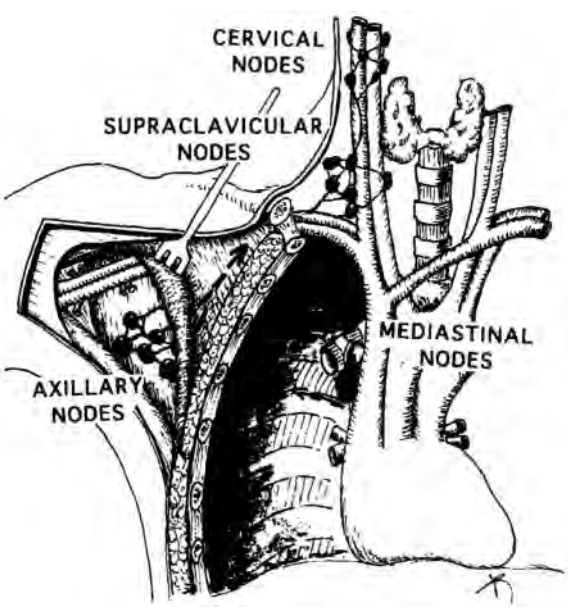

Fig.8.5 - The pathways from a bronchial tumor and mediastinal nodes towards axillary and supraclavicular nodes

Axillary lymph node involvement can occur by two mechanisms (fig.8.5). Chest wall invasion allows malignant cells to travel to the axillary region and retrograde spread mechanism, from the supraclavicular nodes is the second mechanism at least for ipsilateral nodes. Contralateral involvement is invariably associated with involvement of mediastinal or contralateral supra-clavicular nodes (Marcantonio et al.).
Smith et al. have reported on 10 patients with small-cell cancer where the first relapse occurred in the upper abdomen within the paracaval, coeliac or pancreatic nodes.
Presenting with a typical jugular foramen syndrome, a patient (M48) was found to have a mass in the space below the jugular foramen with osteolysis of the skull base. Cytology revealed an adenocarcinoma and subsequently a chest X-ray confirmed a pulmonary mass (Chao et al.). We would consider this a high cervical node metastasis.

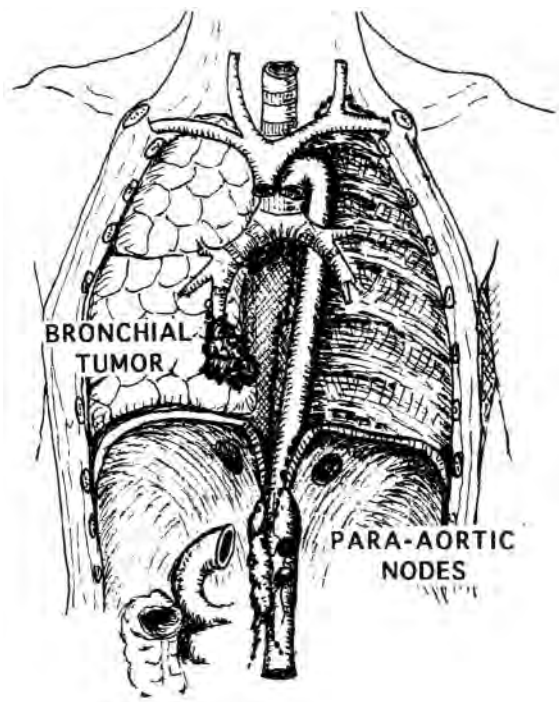

Fig.8.6 - Pathways from a bronchial cancer to para-aortic abdominal lymph nodes

Intra-Thoracal Spread

Bronchial cancer progresses locally within the bronchial lumen, resulting in obstruction and retro-obstructive atelectasia. Other tumors invade the pulmonary parenchyma and even metastasize within the lung.
Some can invade the pleura and cause metastatic nodules, pleural effusion or hemorrhagic effusion, and on rare occasions a spontaneous pneumothorax (fig.8.7) (O'Connor et al.).
Rarely do they can cause tumor emboli either within the lung or in peripheral arteries (see part I). Recently Wong et al. reported on a man (M55) presenting with acute breathlessness. In spite of vigourous treatment, he died and at autopsy, all small pulmonary arteries were found to be filled by (embolic) tumor with an

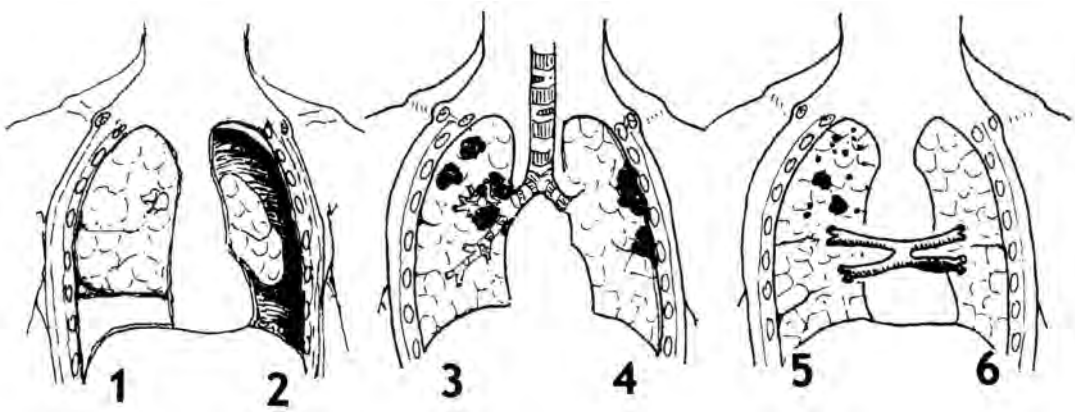

Fig.8.7 - Different pulmonary complications resulting from bronchogenic carcinoma: 1. pleural effusion; 2. spontaneous pneumothorax; 3. intrapulmonary metastases; 4.pleural metastases; 5.vascular tumor emboli;6. tumor thrombus in the vena pulmonalis

ulcerated tumor at the left bronchus of the small-cell type. Another patient (M66) was reported by Nomori et al. as presenting with acute dyspnea due to a large epidermoid tumor that had obturated both pulmonary artery and vein and the left atrium.

The radiological characteristics of pulmonary infarction associated with bronchial cancer have been reviewed by Nomori et al.

1. the pulmonary shadows are at the periphery of the same lobe of the primary;
2. the peripheral shadow appears rapidly and may or may not gradually decrease in size;
3. smaller infarctions 10-25mm in diameter are in the subpleural zone or away from the pleural, round or polygonal in shape, blurred at the margin and demonstrate a centrally directed linear shadow;
4. larger infarctions show a broadly based parenchymal density with truncated apex, convex border, centrally directed linear shadow and a central lower attenuation.

At CT, typical findings will be a shadow located at the same lobe as the tumor and in the periphery, an ill-defined nodular shadow of about 10-25 mm and a lesion located both in the subpleural zone and distinct from the pleura (Yoshida et al.).

Bronchogenic carcinoma causes perfusion defects commonly mistaken for pulmonary embols on radionuclide scans (Marriott et al.). Several mechanisms can be involved.

1. The blood supply is compressed by the tumor. This is the obvious as bronchogenic carcinoma involves the arteries in 18% of cases and the lobar and segmental arteries in 53%.
2. Replacement of the pulmonary arterial flow by bronchial circulation may cause a perfusion defect.
3. Abnormal perfusion may result from a region of obstructed ventilation.
4. Retro-tumoral air-trapping may raise the intra-alveolar pressure above the pressure of the pulmonary artery, resulting in a lower blood flow.

Rarely observed and discussed is the occurrence of pulmonary lymphangitis in patients with bronchial cancer occurring as intrapulmonal spread of the malignancy. The radiology can be misleading towards an extrathoracal primary, but this condition should be taken in account for a bronchial cancer, as the case reported by Fujita et al. has demonstrated.

Pleural effusions in bronchial cancer will be ipsilateral. They may be the first sign of a cancer, but can also be asymptomatic, depending on the volume. They are readily found with chest radiography (Sahn). A tumor occluding the main bronchus is frequently associated with mediastinal involvement leading to complete opacification with pleural effusion because of mediastinal lymph flow obstruction (see Part I).

Intrapulmonary metastases were found in approximately 10% of the patients in the series of Kobayashi et al. Marom et al. recently reported on a series of 27 patients presenting with pulmonary nodules as first presentation of an unknown bronchial cancer. This reveals that bronchial cancer can also present with multiple pulmonary nodules first, with 70% as adenocarcinoma.

Presenting with recent dyspnea and a chest-X-ray showing a prominence at the right hilus, a F43 progressively deteriorated, with a clinical picture of recurrent multiple emboli. According to Gonzalez et al., this condition may be assumed relatively frequent (about 10%), particularly from adenocarcinoma. At autopsy, an adenocarcinoma at the right lower lobe was found, associated with organized thrombi in its vessels,

while most small pulmonary arteries showed marked initial proliferation with severe narrowing (Raper et al.).

Distant Metastases

The extreme contiguity of pulmonary tissue and of the tumor as well, with a rich vascularisation including large vessels, means that there is a high probability of shedding malignant cells into the general circulation. The number of distant metastases is relatively high in the early phase and many bronchial cancers are diagnosed by their metastases before the primary is symptomatic or large enough to be detected on screening chest X-rays.

Table 8. 21 - Unknown Bronchial Cancer
Symptomatology - Metastases before Autopsy (N=28)
Data of Cary et al.

Central Nervous System		7
Any bone metastasis		6
Gastrointestinal (incl. .liver)		5
Other sites		10
Malignancy NOS	3	
Inguinal Node	1	
Infection	3	
Pericarditis	1	
Pleuritis	1	
Aneurysm	1	

In most series, a number of cases have been included where the diagnosis was made after a metastatic site became evident. We will see later that many patients had their bronchial cancer revealed a metastasis at any site. On the other hand, when autopsies are performed, the diagnosis of a bronchial cancer is regularly made, even though the patient was supposed to die of an apparently unrelated disease or from a so-called metastasis of an unknown primary.
In such series, bronchial cancer is discovered in about 25% of them. Performing systematic autopsies, Clary et al. reported that of all final diagnosis, 7% of the bronchial cancers were only detected at autopsy. The distribution of the metastatic sites who became evident before dead is interesting (table 8.21). The usefulness of autopsy is once again demonstrated.

Table 8.22 - Bronchogenic Carcinoma
Site of Solitary Metastases N= 97 of 647 (14.9%)
Data of Deeley et al.

	Total	Percent Solitary
Brain	109	20%
Vertebrae	162	4
Other Bones	94	7
Liver	265	9
Adrenals	214	7
Kidneys	100	8
Pancreas	79	3
Stomach	18	6
Eye	2	--
Supraclavicular Nodes	87	11
Cervical Nodes	78	4

Particularly interesting data were reported quite long ago by Deeley et al. (1969). They investigated 647 necropsies and studied those patients with only one metastasis, giving an insight into the 'shower' of metastases departing from the bronchial tumor (table 8.22). The brain would appear to affect in most cases, but this can be trelated to the the brain recieving a large part of the cardiac output.
If a repartition according to histology type is done, it will be seen that epidermoid cancers have double the number of solitary metastases (table 8.23).

Table 8.23 - Bronchial Cancer
Solitary Metastases according to Histology
Data of Deeley et al.

	N with Extrathor.M.	%Solitary
Epidermoid	144	27%
Oat Cell	175	19
Anaplastic	140	14
Adenocarcinoma	43	14
Total	502	19

Metastases to the Brain

Primary bronchial carcinoma metastasizes earlier and more frequently to the brain than other primary tumors. The reason is most probably that the tumor is able to invade the pulmonary vessels at an early stage and spread its cells unfiltered by the lung capillary bed. It is therefore not unusual for metastases in the brain to become overt even when the primary is small and asymptomatic (type 1 metastases). As discussed in the chapter on brain metastases, bronchial carcinoma accounts for 15% up to 70% in the reported series. This must be related to the type of patients studied.
In a prospective study of 40 patients, MRI was able to detect brain metastases in 11 or 27%, of whom 3 had no relevant symptoms (VandePol et al.).
In spite of the fact that there are numerous reports on the diagnosis and treatment of these metastases from bronchial carcinoma, almost none reports the anatomical distribution of the metastases within the brain (Table 8.24).

Table 8.24 - Bronchogenic Carcinoma
Site distribution of brain metastases (N=231)
Patients having undergone craniotomy
Data of Wronski et al. 1995

Onset of metastases		synchronous	37.2%
		metachronous	62.8%
Number of metastases		single	86.6%
		multiple	13.4%
Site		supratentorial	87%
		left hemisphere	40%
		right hemisphere	47%
Regional distribution			
Frontal	69	Parietotemporal	4
Frontotemporal	3	Occipital	25
Frontoparietal	18	Temporal	9
Parietal	48	other areas	12
Parietooccipital	16		

From this table, the high number of synchronous metastases or those present at diagnosis is immediately obvious, as well as the relative high number of metastases located in the anterior brain regions. However, the findings must be compared with autopsy studies, as there might be a selection bias in craniotomy series. Solitary metastases are more amenable to surgery than multiple metastases.
Radiotherapy series include more multiple metastases, making comparison difficult (table 8.25).

Table 8.25 - Bronchogenic Carcinoma
Site distribution of Brain metastases

	Nieder 1994 N=154(')	Hsiung 1998 N=131(')
Frontal	22.1%	64.1%(°)
Parietal	28.6	80.9
Temporal	13.6	53.4
Occipital	15.6	58.8
Cerebellum	13.6	28.2
Thalamus	3.9	---
Brain stem	2.6	5.3

(') :radiotherapy series;
(°) most patients had multiple metastases

We did not find any reports relating the anatomical distribution to the histology of the primary.
Tomlinson et al. have stated that in a series of 100 patients, neurological presentation occurred in 86.6% of the apical, 61.5% of the peripheral, 42.9% of the intermediate and only 27.7% of the tumors arose in the main bronchus.

Solitary cerebellar metastases are uncommon. Nevertheless, in one institute, Weisberg could collect 16 cases. In 11 cases the neurological symptoms preceded diagnosis of the malignant tumor, but the histology was not reported. As previously mentioned (in the chapter on CNS-metastases), symptoms relating to a bronchial primary are not necessarily present.

Table 8.26- Bronchogenic Carcinoma
Revealing Cerebral Metastases

Author/Yr	Number-Histology	Site
Boumghar 1987	17 cases (non-small)	no data
Ludwig 1987	7cases 7small	Occ.4- Par2 Centr1- Multiple 2
Salvati 1991	M55 Ri.Occipital rev. adenocarcinoma	
Trillet 1991	37 cases 11small/26 NS	No data
Croisile 1992(')	37 cases 11 small/26 NS	No data
Salvati 1994	35 cases Front40%, adeno17/squam15	Pariet 10% Cerebell 11% Te.Par.Oc 17 Occipital 4%
Duval 1996	1 case M50 (calcified) Undifferentiated carc.	Multiple
Latief 1997	31 cases 3 small/28 NS	no data
Dibiane 1998	1 case F47 calcified Undifferentiated carc.	Multiple

Table 8. 27 - Cancer of the Bronchus
Non-Cerebral CNS Involvement
Published Cases

Author	Pat.	Histol.	Complaint	Interval
Sinuscavernosus				
Mills 1981	M59	Undiff.	Ptosis upper lid	Simult
Brain Stem - Midbrain				
Moffie 1980	M65		Diplopia	Reveal
Delaney 1983	M57	Adeno	Weakness-Dysarthria	2yrs
Tomita 1984	M43	Adeno	PalsyIII	Autopsy
Tomita 1984	M64	P.Diff	Diplopia	Autopsy
Keane 1984	M63	Epid.	Diplopia	3 mo
Simpson '87	M58	Adeno	Ataxia	Reveal
Johnson '89	M47	Adeno	Diplopia	4 mo
Ishikawa '97	M39	MDiff	PtosisU.L.Diplopia	Reveal
Corne 1999	M67	Adeno	Hypercapnea	Reveal
Cerebellopontine Angle				
Toye 1993	F38	P.Diff.	Otalgia-Deafness	Reveal
Ventricular				
Barbizet '81	M50	Anapl.	Seizure Syncopes	6 mo
Kart 1986	M61	P.Diff	'Staging'	Simult
Struk 1995	F47	Large	HeadacheDiplopia	Autopsy
IntraMedullary				
Péquignot '77	M63	Small	'Polyneuritis'	Reveal
Hirose1980	M57	Epid.	Neck pain Hoarse	Autopsy
Moffie 1980	M65		Transv.Paresis	Autopsy
Weissman'86	M48	Small	Leg weakness(°)	6 mo
Murphy1983	F58	Small	Neck pain Hemipar	8 mo
Murphy1983	F54	Small	Neck pain Parapares	12 mo
Murphy1983	M45	Small	Neck pain Hemipar	6 mo
Murphy1983	M62	Small	Paresthesia	Simult
Reddy 1984	M64	Small	Incontinence	10 mo
Winkelman'87	M49	Small	Paraparesis	13mo
Chermann '92	F68	Epid	Paraplegia(')	2 mo
Ferroir 1995	F68	Small	Paraparesis	16 mo
Jayasundra'97	M59	Epid.	Shoulder pain	11 mo
Muhlbaur '98	F55	Large	Foot-drop	Reveal
Ferroir1998	F68	Small	Vestibular	1 year
Ferroir1998	M51	Small	Neck pain	1 year
Meningeal Metastases				
Ing 1996	M58	Large	Visual loss	8 mo
Fujita 1998	M58	Adeno	Headache	Reveal
Metastasis to Nervus Trigeminus				
Delaney 1977	M62	Small	Hypoesthesia V	4 mo
Watridge '81	F85	Adeno	Atypical Fac.Pain	Autopsy
Corpus Callosum				
Watridge '81	M64	Adeno	Diffic.Swallow	Simult.

(') at diagnosis cerebellar and cerebral metastasis
(°) also leptomeningeal metastases

Type 1 Brain Metastases

In view of the fact that malignant cells from bronchial carcinoma can reach general circulation early in the growth of the tumor, in a certain number of patients brain metastases are diagnosed before the primary bronchus tumor. This is a common clinical situation in oncology. Several reports have addressed the

problem. Very few, however, give adequate pathology and site data.
The data of Latief et al. give an idea of the incidence of these type 1- metastases for bronchus carcinoma. In 925 patients with a discharge diagnosis of brain metastases, 31 patients had presented with brain metastases, afterwards diagnosed as deriving from a bronchial cancer, or 3.3%. Further data on this group were however not reported. On table 8.26, some data are grouped. All histology types are concerned, but a precise distribution as for example the metastatic site within the brain is impossible to discern.

Reviewing the records of 279 bronchial cancer patients who had undergone brain CT, Tarver et al. could report some data according to the histological type (table 8.27b). The absence of neurological symptoms was no proof of the absence of cerebral metastases, as they were detected in 12%. With vague symptoms, there was a 26% possibility for cerebral metastases. In 64% of the adenocarcinoma, a cerebral metastasis was found, while only in 33% of the squamous cell cancers.

Table 8.27b - Cancer of the Bronchus
Histology and Incidence of Cerebral Metastases at CT
Data of Tarver et al.

	Symptomatology			Overall
Histology N	None	Clear	Vague	
	N=92	N=23	N=27	N=279
Oat cell	11%	96%	30%	28%
Squamous	0	87	16	33
Adenocarcinoma	40	100	36	64
Large Cell	(0/5)	(4/4)	(1/3)	23

Metastases to the CNS (except cerebral)

It is well known that several cancers, notably bronchial cancer can present with uncommon signs due to the involvement of particular sites of the central nervous sytem. Leptomeningeal carcinomatosis is relatively frequent in small-cell cancer (see further). Several other sites deserve some attention, as the symptomatology can be very misleading.
Ophthalmoplegia is a regularly occurring first sign that can lead to either meningeal infiltration, brainstem or ventricular metastases and parasellar involvement. It is quite evident that most reports date from the period CT became available (table 8.27).
The intramedullary metastases would seem very common, as several cases particularly for small cell cancers (10/13) have been reported. A 1986 review found 28 cases reported between 1978 and 1986. It has been postulated that increased CSF pressure resulting from communicating hydrocephalus due to local metastases should dilates or 're-opens' the central canal and provide an alternative route for CSF flow and cell dissemination (Weissman et al.).
Intramedullary metastases are probably underreported, while the symptomatology will be 'hidden' behind several other metabolic and neurological complaints. It is noteworthy that Sherbourne et al. have reported three cases where the clinical presentation was a clear spinal cord problem and where only at autopsy (pre-CT-era) were the metastases in the cord confirmed and the diagnosis of a bronchial primary made, twice a small-cell and one adenocarcinoma.

Watridge also reported a man (M80) developing excruciating pain in the right thigh. At myelography, a large intradural lesion at L2 was found, confirmed at laminectomy as metastatic infiltration of the nerve roots L1-L2-L3.

Leptomeningeal carcinomatosis is a common complication of bronchial cancer. Chamberlain et al. have reported on 32 patients with non-small bronchial cancer. The presenting sign was relatively variable as is usually found in this situation. Headache (11 cases), cranial nerve palsies (9), ataxia (5) and cauda equina syndrome (3) were most frequent.

Several series have been reported for small-cell cancers. It can be asumed to have developed in about 20% of the patients at follow-up (Aroney et al.). About half of the patients with a metastatic site will have meningeal carcinomatosis and in one-quarter it was the only metastatic site. At autopsy it could well amount to 15-20% of all patients (Bunn et al.).

Table 8.28 - Small-Cell Bronchial Cancer
Anatomical Areas Involved (N=60)
Data of Rosen et al.

Cerebrum	N=41
Cerebrum only	27.5%
plus cranial nerves	5.0
plus spinal roots	27.5
plus both	10.0
Cranial nerves	N=11
cranial nerves only	2%
plus spinal roots	2%
Spinal Roots	N=400
alone	28%

Table 8.29 - Small-Cell Bronchial Cancer
CNS-Metastases - Symptoms and Signs (N=60)
Data of Rosen et al.

Cerebral (N=41)		Spinal Root (N=40)	
Headache	6	Nuchal rigid-pain	1
Mental alterat.	36	Back pain	11
Dizziness	1	Weakness of limb	34
Nausea/Vomiting	2	Sensory loss	13
Seizures	0	Sphincter probl	12
Ataxia	2	Paresthesia	6
Cranial nerves (N=11)			
II	2	VIII	1
III-IV-VI	4	IX-X	2
V	1	XI-XII	2
VII	6		

A detailed study of leptomeningeal carcinomatosis in small-cell bronchial cancer was reported by Rosen et

al. It was documented in 60, or 11%, of 526 patients. The cerebral surface and the spinal roots were equally involved (table 8.28). Symptomatology as is usual very variable (table 8.29). Mental alterations and weakness of the lower limb were the most frequent symptom observed, while the facial nerve was apparently the most frequently involved. Metastatic spinal cord compression is well known to also occur in bronchial cancers. Reports specifically addressing bronchial cancer as primary are rare, however. They occur in all histologies, with half of them being from small cell cancers. The most frequently involved site was in the upper thoracic region, as was seen in a series of 102 patients (Bach et al.). Sites did not differ appreciably with histology, except that there was a slightly higher incidence of thoracic ones in the large-cell group. Loss of sensation below the involved level was much more common in the epidermoid group. Pedersen et al. have reported on a series of 29 cases from small-cell bronchial cancer out of a series of 817 consecutively treated patients, or 3.5%. One third (7/22) were located at the lower thoracic half. In 10 patients, spinal cord compression was present at diagnosis. Similar data were later provided by Ampil et al. on 16 patients with-small cell cancers.

Intradural metastatic spread is hardly mentioned in the literature for bronchial cancer. Struk et al. reported on a F47 with drop metastases at level T10 from a large cell cancer. The same patient was found at autopsy to have also pituitary and intraventricular metastases.

METASTASES to TUMORS

As mentioned in Chapter 7, metastases to tumors are rare but described.
They are usuallly diagnosed at autopsy, but better imaging possibilities can provide clues for a diagnosis. Reviewing the literature, the preponderance of adenocarcinoma metastatic to meningioma (8/20) is obvious (Bhargava et al.). Meningioma would appear to a frequent recipient of metastatic tumors.

Several reasons have been postulated for this association.

- the highly vascular structure of the meningioma could result in a higher susceptibility;
- the indolent growth of the meningioma provides a prolonged exposure to metastatic cells;
- the low metabolic rate is do nor foster the growth of metastatic cells;
- the high collagen and lipid content of the meningioma results in a 'fertile' soil.

Symptomatology is no different from other brain tumors, but imaging may give some indication.
One case of metastases from an adenocarcinoma in a thyroid adenoma (Mizukami et al.) from a small cell carcinoma in a renal cell carcinoma has been reported (Kwak et al.).

Metastases to the Kidney

Quoted as the most frequent source of renal metastases, bronchial cancers have a high metastatic rate to the kidney. Some autopsy studies state that it is the most frequent site.
Despite this, no systematic review of the pathology of renal metastasis has appeared. Most reports state that they are located at the periphery of the kidney and bilateral in 75%.
Ollson et al. (1971) found renal metastases in 60 of the 315 autopsied cases or 19.1%. The right kidney was involved in a ratio of 3:1 and 60% were bilateral.

The revealing symptomatology will rarely be hematuria, but fever due to an abcess-like evolution is not uncommon. Progressive destruction of both kidneys has also been reported.
Pain in the flank disclosed at US-graphy a renal mass in the lower pole of the left kidney in a M61. FNAC demonstrated a squamous cell carcinoma of an unknown bronchial cancer (Chippindale et al.).

Metastases to the Bone

Skeletal metastases are common in bronchial cancer. They amount at autopsy to 25-30% of the cases. However, data on the anatomical site distribution are not available, except for a report dating back to 1966 and prior to the 'Strontium-era' (table 8.30) and of Morgan et al. (table 8.31). Overall 45% is located within the spine and 28% in the thoracic bone and skull.
Osteoblastic metastases (Miyazaki et al.), cystic metastases even at the skull (Gray et al.) and a series of enchondral (cortical) metastases (Deutsch et al.) have only rarely been reported.

Table 8.30 - Cancer of the Bronchus
Bone Metastases - Anatomical Site (N=61 patients)
Data of Amalric et al. 1966

Skull	5.8%	Pelvis	10.4%
Shoulder	7	Humerus	4.7
Ribs	10.4	Femur	9.3
Cervical Spine	8.1	Other long bones	2.4
Thoracic Spine	17.4	Other bones	4.7
Lumbar Spine	19.8		

Table 8.31 - Cancer of the Bronchus
Anatomical Distribution of Bone Metastases (N=41)
Data of Morgan et al.

Skull	46%	Pelvis	68%
Spine	76	Femur	41%
Ribs-Sternum	71	Distal Leg	2%
Shoulder	24	Distal Arm	2%
Humerus	29		

Some rare metastases to the patella were reported, one as first symptom (Pazzaglia et al.), in one patient even bilaterally and simultaneous (Pauzner et al.).

Many reports discuss the overall metastases frequency, though none are able to discern a particular preference for a particular anatomical site.

The bone marrow is an important metastatic site in bronchial cancer, especially for the small-cell group. Tumor cells were observed in the bone marrow in 18 of the 139 patients with non-small cell cancer, or 13%. The authors however, did not report on any follow-up of these patients, making it a matter of debate wether this test might be relevant to selecting patients for adjuvant chemotherapy (Pantel et al.).
This metastatic site was intensively studied for small cell cancer, but reliable data are largely absent. In their study of 35 consecutive patients, Trillet et al. noted that MRI was able to detect metastases in 10 of 26 patients, where routine methods had produced negative results. MRI was also the most sensitive method in the series of Hochstenbag et al. MRI was positive in 12 patients with normal scintigraphy and in 14 with normal bone marrow aspiration biopsy.
A study of 100 patients was recently reported by Imamura et al. At diagnosis they observed with MRI lesions in 35 patients. Although the further data were somewhat fuzzy, they concluded that all lesions observed in skeletal scintigraphy were preceded by a positive site at MRI, demonstrating that bone marrow lesions precede osteolysis.
Using a specific immunotyping, Cote et al. detected micrometastases in 40% (17/43) of the small-cell cancer patients, with 29% at stage I-II and 46% ar stage III. The study concluded that there was an increased risk for recurrence in cases of metastases, but no anatomical study was done in follow-up.

The recent report of Paspati et al. is worth mentioning. They discovered a vertebral anomaly on a bone densitometry, which turned out to be a metastasis from a non-small cell bronchial cancer.

Acral - Distal Bone Metastases

Bronchial cancer is a frequent source of acral metastases. About half of the reported cases in the literature are due to this primary. A literature review of up to 1980 by Nagendran et al. found 33 cases with metastases in the hand. There is no preferential site.
Several cases have been reported where skeletal metastases occurred in the distal (acral) bones. Some were even first sign (Type 1) metastases (table 8.32).
As has been mentioned in Part I., the metastases in the hand are located in the phalanges, while the metatarsals are the most frequent site in the foot. Why should this be so?

A patient (M79) presented with knee pain. Patellar metastases from an unknown small cell bronchial cancer were found (Buckley et al.).
Aside of phalangeal metastases and hypertrophic osteoarthropathy, poly-arthritis mainly of the knee developed in a woman (F61) associated with a radiological diagnosis of bronchial cancer. Only at autopsy were several blood vessels in the synovia of the knee found to contain carcinomatous cells, confirming the rare occurrence of malignant metastatic arthritis (Fam et al.). Mellaerts et al. recently reported on a M61 presenting with a monoarthritis at the first metatarsophalangeal joint. Cytology disclosed large-cell or epidermoid carcinoma. A new CT of the thorax confirmed a tumor mass at right apex, associated with mediastinal nodes.

Table 8. 32 - Cancer of the Bronchus
Acral Bone Metastases reported

Hand				
Vaezy 1978	M52	Epidermoid	Ri.IV Mid Ph	Reveal
Nissenbaum'78	M46	Anapl.	Os Hamatum Ri.	Revea
Cary 1981	M54	'Carcinoma'	Carpus (2x)	???
Birkholz '82	M54	Epidermoid	Le.V,RiII (°)	3mo
Khokhar '83	M67	Epidermoid	Ri.Mi.Dist.Ph.	Reveal
Rose 1983	M53	Epidermoid	Le. II Dist.Ph.	Reveal
Cross 1985	M74	Epidermoid	Ri.I dist Ph	Reveal
Gottlieb '85	M68	Epidermoid	Whole Carp	Reveal
Letanche '90	M53	Undiffer	Carp.+MetaV	Stag
Letanche '90	M59	Epidermoid	III.Mid Ph	2mo
DeMaes.'95	M60	Epidermoid	Ri+Le thumb	3mo
DeAbbafy '98	M54	LargeCell	Ri.V prox.Ph.	4mo
Baran 1998	M70	Carcinoma	Le. III Dist.Ph	2mo
Foot				
Vaezy 1978	M48	Epidemoid	Ri.big toe	2mo
Birkholz '82	M54	Epidermoid	Ri.big toe(°)	3mo
Eggold 1985	F67	AdenoCa	Le. V	1 yr
Aellen 1990	M68	AdenoCa	Ri. MetaT I	Reveal
DeMaes.'95	M60	Epidermoid	Ri. big toe (')	3mo
Wu 1995	F40	Epidermoid	Le. MetaT III	Reveal
Wu 1995	M47	Poorly Diff	Le. Hallux dist	Imo
Kemnitz '96	M68	AdenoCa	Le. MetaT I	Reveal
Koss 1996	M52	Poorly Diff	Dist.Tibia	Reveal
Delgadillo'98	F42	SmallCell	Ri. MetaT III	Reveal
Jänne 1999	F35	AdenoCa	Ri. MetaT.IV	Reveal
McGarry 2000	M45	'Cancer'	Ri. Calcaneum	Reveal

(°) case report as metastatic to maxilla
(') same patient mentioned above for hand

Metastases to the Gastrointestinal Tract

All parts of the gastrointestinal tract can be involved in a metastatic process from bronchial cancer. The small intestine, especially the jejunum, is the most frequently concerned. Many patients however have other less prominent metastases, stressing the fact that it is frequently part of a widespread process.

Metastases to the esophagus must be differentiated from the more frequent contiguous invasion occurring through expansion and invasion from the primary, as both tracts are adjacent to a large length within the mediastinum or secondary mediastinal lymph nodes.
Hansen et al. have reported on six patients with an asymptomatic bronchial cancer presenting with esophageal 'disease'. All histology types were involved. As we have mentioned in Chapter 3, esophageal compression leaves the mucosa intact and can mislead the

radiologist and the endoscopist.
Diagnosis of leiomyoma, benign stricture, duplication cyst, achalasia and primary cancer of the esophagus were made. Esophageal findings in the subcarina part should raise suspicion of a bronchial cancer and adequate workup made.
Some reports have mentioned true esophageal metastases. A type 1 or revealing metastasis was reported by Inoshita et al. A patient (M65) presented with serious dysphagia. Investigation led to theinitial diagnosis of an intramural leiomyoma, but at surgery a peripheral bronchial carcinoma was found, the primary of the esophageal metastasis.

Stomachal metastases are relatively rare, although an autopsy series mentioned by Turner et al. revealed 64 cases in 912 patients with bronchial cancers, or 7%. Of the 21 patients studied, only the mucosa and submucosa was involved in 13, while all layers had been invaded in 6. In nine or about half, multiple lesions were found.
Gastric perforation is not common, and only a few cases have been reported (Fletcher). Two cases have been reported where the first symptom was gastric pain or ulcer revealing a metastasis from a bronchial cancer, both of the epidermoid type (Morton et al.;Tawney et al.). They are probably not the only ones. Another was diagnosed at endoscopy as being a large cell cancer (Borsch et al.).
Most patients present with a bleeding ulcus, and at radiology the typical 'target' or 'bull's eye lesion is usually found (Rubin et al.).

A few cases of duodenal metastases have been described (Raijman). One revealing case was reported by Lagrange et al., where gastroscopy diagnosed a bleeding malignant ulcer in the duodenum from a large-cell cancer. The case reported by Hinoshita et al. was also from a large cell cancer, with the duodenal bleeding occurring within a week of lobectomy.
A malignant duodenocolic fistula was mentioned by McNeill et al., but it is not clear if this originated in the duodenum, or in the more frequent site of the colon.
Another fistula, from the mesenteric artery to the duodenum was the cause of bleeding, and occurred three years after resection in a M55, from a metastatic anaplastic bronchial cancer (Steinhart et al.).

The small bowel is the most frequently involved segment of the GIT in bronchial cancer. In 218 autopsies of non-small cell lung cancers, 10 patients with small bowel involvement were detected, or 4.6%. The patients involved all had inoperable tumors and several other metastases (Stenbygaard et al.). However, Woods et al. reporting on 13 patients operated under emergency conditions, concluded that many had solitary lesions and palliative surgery could obtain relatively long survivals.
Reviewing the literature up to 1991, Mosier et al. retrieved 34 cases and added 3. The pathology features reviewed are in Table 8.33. Perforation occurred in more than half and the most involved part was the jejunum. Epidermoid cancers were in the majority.

Table 8. 33- Cancer of the Bronchi
Small Bowel Metastases (N=37)
Literature Review in 1992 by Mosier et al.

Histology		Operative Finding	
Epidermoid	49%	Perforation	57
Large Cell	33	Obstruction	34
Small Cell	11	Bleeding	6
AdenoCarcinoma	3	Mass	3
Other	1		
Presenting Symptoms		**Site**	
Abdominal pain	86%	Jejunum	79%
Vomiting	26	Ilieum	21
Melena	23		
Weight loss	16		
Dizziness	6		

Curiously, a number have presented with symptoms of metastases before diagnosis of the primary. They are listed on Table 8.34. A few rare cases have been reported presenting with intussusception (Issa et al.). They found only one other case in the literature.
The review by Pang et al., who found that of the 11 cases reported on intestinal metastases, 7 or 63% were in patients with a lower lobe bronchial cancer, is troubling. This needs further data. When we tried to retrieve data from the case reports on the primary location, more than half did not provide enough to establish some relation ship. However, when mentioned, the lower lobe bronchial cancers were not the main ones.

Table 8.34 - Cancer of the Bronchi
Small Bowel Metastases as First Sign
Cases Reported

Author	Pat	Histology	Presentation
Doutre 1980	M63	Epidermoid	Obstruction
Leidich 1981	M76	Epidermoid	Perforation
Gonzales '83	M66	Adenocarc	Occult bleeding
Quayle 1985	M78	Epidermoid	Perforation
Listrom 1988	M63	Epidermoid	Intussusception
Kabwa 1996	M62	Epidermoid	Subobstruction
Berger 1999	F56	Large-Cell	Melena

Appendiceal metastases are very rare, also for bronchial cancer. Presenting as acute appendicitis, the two cases we are aware of tur,ed out to be adenocarcinoma and both had several other metastases (Gopez et al.). The case of Haid et al. should be considered as a colonic (cecal) metastasis. On the contrary, appendiceal metastases seem more frequent in small-cell carcinoma (Table 8.35).

Metastases to the colon would appear to be unusual (Table 8.36). An incidence of 5% has been stated (Smith et al.). Symptoms of obstruction due to annular growth and/or chronic bleeding with anemia were

the most frequent symptoms. Some patients presented with colon metastases as first manifestation of an unknown bronchial cancer.

Table 8.35 - Small Cell Cancer of the Bronchus
Metastases to the Appendix
Case Reports

Author	Pat.	Histol.	Interval
Pang 1988	M47	Small-cell	11 months
Gonzalez 1996	M65	Small-cell	3.5 years
Wolf 1999	M71	Small-cell	6 months

Table 8. 36 - Bronchial Cancer
Metastases to the Colon Reported

Author	Pat	Histology	Site	Interval
Smith 1978	M52	Epidermoid	Mid Sigm	Simul
Smith 1978	M57	Epidermoid	Sigmoid	2 yrs
Brown 1980	M63	Large-Cell	Sigmoid	Simul
Wegener '88	M69	Small-Cell	Ascend	Simul
LeMay 1992	M70	Small-Cell	Ascend	Simul
Gateley 1993	M68	Epidermoid	Sigmoid	9 mo
Mirallie 1993	M44	AdenoCa	Ascend	6 mo
Johnson 1995	M50	Small-Cell	Rectum	2 yrs
Carr 1996	F60	Epidermoid	Splenic Fl	1 yr
Carr 1996	F52	Adeno-Sq	Splenic Fl	6 mo
Bastos 1998	M69	Epidermoid	Sigmoid	2 mo

It should be noted that most of the cases (5/11) had an involvement of the sigmoid.

We are aware of only one case reported with an anal metastasis. A M75 presented 3 months after lobectomy with anal bleeding through a polypoid lesion. Squamous cancer was disclosed of the same aspect as the primary bronchial (Kawahara et al.).

Metastases to the Hepato-Biliary System

Although cited as a common site of metastases, data on precise incidence, intrahepatic distribution, pathology and number of metastases are largely absent in the literature.

Hepatomegaly was found at presentation in 21% of 157 consecutive patients with small-cell cancer. An abnormal CT scan was found in 23% and an abnormal radionuclide scan in 22%. Overall, 26% had liver metastases (Mulshine et al.).

Acute and fetal hepatic failure was reported in four patients with small-cell cancer, with two of them not known to have a bronchial tumor. The authors could retrieve 13 other cases from the literature (MacGuire et al.).

A few cases have been reported as presenting with hepatic rupture (Mittleman), calcifying metastases at CT (Baliko et al.) and paradoxal increased multi-focal uptake at radionuclide scintigraphy with Tc-99m phytate (Chang et al.).

Seventeen months after palliative radiotherapy for an epidermoid carcinoma, a patient (M69) presented with right upper quadrant pain. Eventually at laparotomy, the wall of the gallbladder was found to have been replaced by metastatic tumor tissue, though there was no other abdominal problem (Gutknecht).

A case with massive intra-hepatic metastases causing biliary obstruction was reported by Obara et al. Together with large supraclavicular nodes, it was the first sign of bronchial small cell cancer.

Metastases to the Pancreas

In autopsy series, metastases to the pancreas are claimed to account for less than 5% of the cases. Before the CT era, they were difficult to diagnose unless obstructive icterus occurred. They are much more frequent in small-cell cancers.

A few case reports have been published where solitary metastases were detected.

At autopsy of 250 cases of bronchial cancers, Lankish et al. found 14 patients, or 5.6% with any pancreas metastases. Twelve were from a small-cell cancer or 86% of those with a pancreas metastasis. Pancreatitis was present in 3/14 or 21%.

A retrospective study involving 850 patients, revealed 26 or 3.1% with a metastasis to the pancreas (Maeno et al.). In 19, it concerned a single nodule, with 12 located at the head (Table 8.37).

The diagnosis was obtained at presentation in 6, while it was arrived during follow-up in the others within a mean interval of 6 months. In all patients other metastatic sites were involved.

Table 8.37- Cancer of the Bronchus
Metastases to the Pancreas N=26
Series of Maeno et al.

Histology		Pathology		
Epidermoid	3	Solitary		19
Adenocarcinoma	9	Head	12	
Large-Cell	1	Body	4	
Small-Cell	13	Tail	3	
		Multiple		3
		Diffuse		4

A common feature of several reported cases was the symptomatology of pancreatitis at presentation as clinical presentation of the metastasis. This is not uncommon in small cell cancer metastatic to the pancreas (Stewart et al.). A case presenting with pancreatitis as first and sole manifestation has been reported by Noseda et al. The diagnosis was made by FNAC after an ERCP had shown several stenoses in the pancreatic duct.

A M56 presenting with a somatostatinoma syndrome was reported. Only at autopsy an oat cell tumor of the bronchus was disclosed with metastasis in liver and pancreas (Ghose et al.).

Adrenal Metastases

In autopsy series, metastases to the adrenals amounted to 45%, in small cell cancers even more. Hidden in the retroperitoneal space, they are nowadays readily visualized and detected by CT. The sensitivity of CT is, however, somewhat low unless clearcut features are

visible (Andersen et al.).
They are usually asymptomatic, but in particular cases, hemorrhage in the retroperitoneum, pain and extreme adynamia (Addison's crisis) have been reported even as first sign of an asymptomatic bronchial cancer (table 8.38).

Table 8. 38- Bronchial Cancer
Presentations with Symptomatic Adrenal Metastases

Author	Pat	Histology	Complaint	Interv
Hill 1965	M34	'Cancer'	Addison Crisis	Simult
Guzzini 1989	M59	Small-cell	Addison Crisis	3 yrs
Guzzini 1989	M66	Adenoca	Addison Crisis	1 yr
Kung 1990	M62	Adenoca	Addison Crisis	Reveal
Kung 1990	M56	Adenoca	Addison Crisis	Reveal
Yamada 1992	M63	Epiderm.	Mass. Hemorrh.	1 I mo
Berger 1995	M62	Non-small	Back pain	3 mo
Berger 1995	M67	Non-small	Flank pain	Simult
Kinoshita '97	F47	Adenoca	Mass.Hemorrh.	9 mo

In 1965, Hill et al. reviewed the literature and found 17 other cases of bronchial cancer with Addison-crisis reported during their evolution. The diagnosis is probably not immediately evident and the clinical presentation frequently ascribed to widespread metastases.
Adrenal hemorrhages are much more common in adenocarcinomas, as found by Kinoshita et al. who reviewed 9 cases.
Back pain has sometimes also been reported as metastatic sign by rheumatologists.
The incidence of adrenal metastases will depend on stage of disease. In 96 patients, Eggesbo et al. found at CT 8 adrenal expansive lesions in 6 patients. In 205 patients, Silvestri et al. found 30 patients with an abnormal gland, of whom 4 were consistent with an adenoma. The authors found that the presence of adrenal metastases parallels the extent of the disease, as all 26 had at least one other clinical abnormality.

Adrenalectomy was performed in 27 patients by Burt et al., but metastases were found in only 5, underlining the difficulties of interpretation of the images. CT guided biopsy seems a better approach (Porte et al.).

A correlation between the adrenal metastases and the site of the primary in the bronchial tree is not available from the literature. However, all 9 patients reported by Higashiyama et al. and either surgically or palliatively treated had their cancer in the upper lobes. Analyzing 405 cases with adrenal metastases, Karolyi noted that in 234 or 57% they were ipsilateral and in 105 or 26% contralateral. The others had bilateral involvement. When the amount of metastatic sites increased, more bilateral involvement was noted. At least in early stages, these data are compatible with a lymphatic route of spread to the adrenal. The author did not analyze the data acccording to the site or side of the bronchial cancer.

Metastases to the Spleen

Metastases to the spleen are nowadays diagnosed earlier than before the CT era (table 8.39). In autopsy series, they amount up to 10%. In their report on two cases, Kinoshita et al. found 15 or 5.6% with splenic metastases in their autopsy-reports of 267 patients. The incidence was the lowest (1.4%) for epidermoid cancers, 5.7% for the adenocarcinoma, 10.3% for the large-cell and 8.3% for the small-cell cancers. All patients also had metastases in other abdominal organs.

Table 8.39 - Bronchial Cancer
Metastasis in the Spleen - Case Reports

Author	Pat	Histology	Pathol.	Interval
Litvin 1975	F59	Undiff.Aden.	Single	Simult
Turner 1978	M60	Epidermoid*	??	??
Rydell 1978	M48	Large-Cell*	Single	3 mo
Edelman 1990	F63	Adenocarc	Single	Simult
Macheers 1992	F69	Large-Cell	Diffuse	Simult
Silverman 1993	M77	Large-Cell	Single	??
Gupta 1 993	M58	Epidermoid*	Single	Simult
Kinoshita 1995	M76	Epidermoid	Single	18 mo
Kinoshita 1995	F72	Poorly-Diff	Single	Simult
Lee 2000	??	no data(")	Isolated	???

(*) revealed by spontaneous rupture
(") incidental finding with non-oncologic GIT-bleeding

Twelve were macroscopically visible, while in 3, they were only found at microscopy. Of the former 12, six were smaller than 1 cm in size. It is strange that 9% of the left-sided bronchial tumors had splenic metastases and only 3% of the right-sided ($p<0.05$).
One unusual occurrence is spontaneous rupture with hemoperitoneum and acute abdomen, revealing the cancer, particularly bronchial cancers. It should be noted that half of the patients with splenic metastases on the list are female.

Urologic Metastases

A woman (F72) has been reported with a small cell cancer of the bronchus, presenting three months after initial treatment with a hematuria (Coltart et al.). Cystoscopy confirmed a small-cell metastasis at the posterior wall. We are not aware of other cases with bladder metastasis from bronchial cancer
A young man (M23) presented with acute urinary retention. A tumor of the prostate was found with infiltration of urinary bladder and rectum, but a CT of the thorax also disclosed a large tumor at the right hilus. As both biopsies were small cell cancer, a metastasis to the prostate was the diagnosis (Madersbacher et al.).
While such cases are rare, metastases to the penis have been repeatedly reported (table 8.40).

Reviewing the literature, Yokoi et al. found 10 additional cases, mainly in the Japanese literature.
A man (M77) presented with a 'carcinoma en cui-

rasse' of the scrotum and was in a very bad condition. At autopsy metastatic adenocarcinoma of the bronchus was discovered (Ferguson et al.).

Table 8. 40- Cancer of the Bronchus Metastasis to the Penis Reported

Silber 1976	M52	Epidermoid	Autopsy
VanWyk 1983	M54	Large-Cell	Revealing
Schwesinger '86	M45	Carc.Solidum	Simult. (stageIV)
Yokoi 1992	M67	Epidermoid	18 mo
Bonaminio 1995	M67	Epidermoid	2 year
Siam 1998	M67	Epidermoid	13 mo

Cardiac Metastases

Metastases to the heart and pericard are not uncommon. An autopsy series by Kayser et al. produced an incidence of 10.2% (Table 8.41), whileTamura et al. obtained 31.1%.

In the 137 cases, the cardiac involvement was solitary, but one must remember that this happens almost always in cases of contiguous or lymphatic invasion, at least in bronchial carcinoma.

The most frequent site of cardiac involvement is at the pericard. Several cases have even presented initially with a cardiac tamponade. The pathway of cancer to the pericard is through lymphatic invasion from the mediastinal lymph nodes as has been demonstrated by Tamura et al.) (Chapter 1). The relative incidence of the different modes of spread towards the heart is on Table 8.42. The large majority of the cases of cardiac involvement must be ascribed to lymphatic extension.

Table 8. 41 - Bronchial Cancer Metastases to the Heart - (1,345 autopsies) Data of Kayser et al.

Histology		
Epidermoid	8.9%	33.6% of all card.metast.
Adenocarcinoma	9.6%	14.6%
Large Cell carc	9.2%	13.1%
Small Cell	13.2%	38.7%
Site		
Pericard	90.5%	of 137 cases
Epicardium	58.4%	
Myocardium	40.9%	
Left Ventr	41/56 - Right Ventr.	13/56
Left Atr	11/56 - Right Atrium	8/56

Table 8.42 - Bronchial Cancer Types of Cardiac Involvement (74 autopsies) Data of Tamura et al.

	Pericard Eff.	Cardiac
Lymphatic	14	18
Hilar	10	12
Mediastin.	4	6
Hematogenous	1	5
Total	15	23

In another series (Strauss et al.), the influence of histology type was addressed. In 418 patients, cardiac metastases was seen in 104 or 25% (table 8.43). Overall, large-cell cancers seem to have a higher incidence. The involvement of the pericard is more frequent than that of the myocard, as was discussed above.

Table 8.43 - Bronchial Cancer Cardiac Metastases and Histology Data of Strauss et al.

		PeriC	MyoC
Epidermoid	28/229 : 22%	26	11
Small Cell	20/100 : 20%	19	14
Adenocarcinoma	30/110 : 27%	29	12
Large Cell	26/ 79 : 33%	17	10

Another frequent type of cardiac involvement is via intravascular extension from the pulmonary parenchyma through the pulmonary veins into the left atrium. Of all cases reported with such extension, more than half originated from bronchial cancers. A possible difference between left or right-sided cancers was not addressed.

Cutaneous Metastases

Metastases to the skin from bronchial cancer are not infrequent, especially in small-cell cancer.

Mainly due to their dramatic appearance, metastases to the nose tip, nicknamed the 'clown-nose' have frequently been reported (table 8.44) (see Chapter 7).

Several cutaneous metastases are of the revealing type. They can be single or multiple, but most are located along the thoracic wall.

Metastases at the umbilicus (Saito et al.), at the lip (revealing) (DeArgilla et al.) and at the pre-auricular skin (Falk et al.) have been reported.

Metastasis to the hand have been described at the back of a finger (Prystowsky et al.), the fingertip (Sweldens et al.) and to the nail unit (Kegel et al.).

Table 8.44 - Bronchial Cancer Case Reports of 'Clown Nose'

Author	Pat.	Histology	Interval
Gault 1985	F75	Ri. 'Carcinoma'	Reveal
Gault 1985	M67	Le. Epidermoid	Reveal
French 1995	M73	Ri. Epidermoid	Reveal
DeSimoni '97	M58	Le. 'Carcinoma'	Reveal
Gal 1997	M65	Ri. Adenosquamous	2.5yrs
VieiraMonta '98	M63	Le. Anaplastic	Reveal
Hammert 1999	M59	?? Epidermoid	2mo

Table 8. 45 - Bronchial Cancer Skin Metastases Distribution Data of Kamble et al. (N=43)

Scalp, face and neck	49%	Histology	
Chest trunk	37	Adenocarcinoma	45%
Scalp, face, chest trunk	7	Epidermoid	30
Lower limb	5	Small cell	17
Upper limb	2	Other	8

The relatively large series would appear to indicate

that about half of the skin metastases occur in the head (Kamble et al.) (table 8.45). In 73% there was only one skin metastases and the size ranged from 2 to 10 cm with a mean of 4 cm. Other data were provided by Dreizen et al. (table 8.46).

Table 8. 46 - Bronchial Cancer
Skin Metastases Distribution (N=1000)
Data of Dreizen et al.

Incidence according to Histology		
Adenocarcinoma	73/388	18.8%
Large cell carcinoma	6/ 32	18.7
Small cell carcinoma	50/349	13.2
Epidermoid carcinoma	38/231	16.4

Overall according to Anatomic Site (N=167 metastases)			
Scalp	20	Abdomen	15
Neck	32	Shoulder	14
Face	14	Back	13
Chest	34	Upper extremity	8
Breast	2	Lower extremity	12

Table 8.47 - Bronchial Cancer
Head and Neck Metastases reported

Author	Pat	Histology	Site of M	Interval
Vrebos 1961	F56	Epidermoid	Mandible	Reveal
Tucker 1968	M46	Carcinoma	Maxilla	no data
Inalsingh '74	F??	Adenocarc	Base Tongue	17 mo
Solomon '75	M56	Carcinoma	Palate	3 mo
Donoff 1976	M70	Small-Cell	Mandible	4 mo
Donoff 1976	M49	Epidermoid	Mandible	Simult
Donoff 1976	M50	Undifferent	Mandible	Simult
Sanner 1979	M57	Undifferent	Max.Gingiva	2 mo
Maw 1980	M51	Epidermoid	Mandible	2 yrs
Barr 1980	M75	Adenocarc	Mand.gingiva	1 mo
Kaugars 1981	M59	Poor Differ.	Max.Gingiva	Reveal
Compère '81	M48	Epidermoid	Mand.Condyle	Reveal
Donazzan '81	F60	Anaplastic	Mand.Condyle	Reveal
Peacock '82	M53	Epidermoid	Mand.Condyle	Reveal
Gerlach '82	M42	Epidermoid	Mand.Condyle	Reveal
Birkholz '82	M54	Epidermoid	Max.Gingiva	3 mo
Birkholz '82	M51	Epidermoid	Max.Gingiva	3 mo
Birkholz '82	M56	Epidermoid	Max.Gingiva	8 mo
Redman 1983	M55	Epidermoid	Mandible	Reveal
Davies 1986	M80	Epidermoid	Tongue	Reveal
Monforte '87	M25	Adenocarc	Tonsil	Reveal
Seddon 1988	M83	Small-Cell	Le.Tonsil	Reveal
Shalowitz '88	M54	Small-Cell	Parotid Bil.	Simult
Svirsky 1989	M62	Small-Cell	Gingiva Inf	3 mo
Heimann '89	M74	Small-Cell	Le.Tonsil	Simult
Zachariades'89	M62	'Cancer'	Ri.Mandible	1 yr
Staalsen '92	M66	Adenocarc	Gingiva Inf	3 mo
Bernaldez '94	M56	Epiderm	SupraGlottis	1 yr
Shebab 1994	F70	Epiderm	Tongue	2 mo
Peris 1994	M68	Undifferent	Max.Gingiva	Reveal
Storey 1997	M66	Epiderm	Maxilla	4 mo
Marinella '97	M60	Large-Cell	Mandible(')	Reveal
Hisa 1997	M68	Small-Cell	Tonsil	4 mo
Prevost 1997	M66	Undiffer.	Thyroid	Reveal
Hisa 1998	M61	Small-Cell	Parotid	Reveal
Mui 1999	M65	Epiderm	Tongue border	Reveal

(') with numb chin syndrome

There is apparently no significant difference in the incidence according to histology.

Summing up two series containing a total of 40 patients, it was noted that 29 or 72.5% had their primary at the upper lobe (Terashima et al; Coslett et al.). If this is compared to intestinal metastases, the hypothesis could well be made of a 'separate' lymphatic drainage, at least when some blockage at the mediastinum has already occurred.

Head and Neck Metastases

Metastases from bronchial cancer to the Head and Neck region, particularly to the oral cavity are rare. We have collected several cases (Table 8.47). There is a propensity to metastasize in the bony mandible and the gingiva andin particular in the tongue (4 cases). A review of the literature in 1981 disclosed 37 case reports (Kaugars et al.). The majority concerned epidermoid cancers. Fifty percent were first sign or revealing metastasis, but this probably is a reporting bias.

Muscular Metastases

Though rare in any cancer, several have been reported in bronchial cancers. There is apparently no histology nor site preference (Table 8.48).

Table 8. 48 - Bronchial Cancer
Metastases in Muscle Reported

Author	Pat	Histology	Site	Interval
Ramanathan '73	M47	Epiderm	Gluteal	6 mo
Barnard 1975	M70	Cancer	Buccinator	Reveal
Levack 1977	M72	Epiderm	IschioRect	Reveal
Pellegri 1979	M61	Epiderm	Triceps	Reveal
Rondier 1980	M79	Undiffer	Shoulder	Reveal
Sarma 1981	M53	Adenoca	Deltoid	Reveal
Shachor 1986	M47	Anaplast	Forearm	5 mo
Siame 1986	M51	Epiderm	Latissim.	Simult.
Siame 1986	M59	Large-cell	Glut-Psoas	3 mo
Liote 1986	M43	Epiderm	Paraspinal	Reveal
Alburquerque'87	M64	Adenoca	Calf	Reveal
Shridar 1987	M59	Adenoca	Gluteus	Reveal
Shridar 1987	M50	Adenoca	Biceps	10 mo
Shridar 1987	M31	Epiderm	Biceps	2 mo
O'Keefe 1988	M70	Adenoca	Lumbar	Simult
Mignani 1989	M52	Adenoca	Thigh	Reveal
Fernyhough '89	M67	Adenoca	Vastus Med	Simult
Menard 1990	M60	Epiderm	Triceps	1 yr
Menard 1990	M63	Adenoca	Deltoid	Reveal
Judson1990	M68	Adenoca	Shoulder	Simult
Ferrigno 1992	M70	Epiderm	Lumbar	Simult
Toussirot 1993	M39	Adenoca	Gluteus	Reveal
Toussirot 1993	M65	Epiderm	Biceps Brach	Reveal
LeGangneux '94	M54	Adenoca	Paraspinal	Simult
McKeown 1996	M44	Epiderm	Pectoral.	1 mo
Nash 1996	M63	Adenoca	Psoas	Reveal
Nouri 1996	M62	Large-cell	Deltoid	Reveal
Peyrade 1997	M58	Undiffer	Thigh	Simult
Suto 1997	F68	Adenoca	Quadriceps	7 mo
Ohta 1999	M55	Adenoca	Gluteus	8 mo
Rossi 2000	M59	Adenoca	Triceps	6 yrs
Maréchal 2001	M66	Adenoca	Infraspinatus	Reveal

We found 32 cases reported, with 16 adenocarcinomas and 10 epidermoid cancers. To this one could be added the 8 cases recently reported by Glockner et al., four being from an adenocarcinoma. Six were located in the lower extremity.

Not all cases reported were in a late evolution stage, while in several cases other metastases were also disclosed. Nevertheless, it was the presenting sign or reason the for consultation in 13 cases.

It is very probable that there have been many more cases, but as always, those presenting first are more prone to be published, while those occurring in the later phase go frequently undetected or with a symptomatology attributed to other pathologies or metastases.

Symptomatology is always local pain with hindrance to movement. Size is usually large and measuring several centimeters. While CT is useful for deeper sites and evaluation of extension, FNAC or FNAB is a simple method for definite diagnosis.

Ophthalmic Metastases

Compared with other cancers, the main issue with tese metastases is that they occur in all segments of the eye and orbit. Nevertheless they are rare compared with other primaries (table 8.49).

About half of the reported cases were revealing ones.

Witschel et al. have reported on 6 cases of choroidal metastases. In 5, the ocular symptomatology came before the diagnosis of the primary and half of them concerned a small cell carcinoma.

The case reported by Gallie et al. concernd a man presenting with decrease in vision where a bronchial cancer was found at first presentation. The eye was enucleated and retina and optic nerve were found to be involved, without tumor invasion of the choroid.

Table 8.49 - Cancer of the Bronchus
Ophthalmic Metastases Reported

Author	Pat.	Histology	Site	Interval
Ferry 1967	M59	SmallCell	Orbit	Reveal
Sakula 1968	F67	SmallCell	Choroid	5 mo
Gallie 1975	M49	Epiderm	Optic N.head	Reveal
Klein 1977	M52	Epiderm	Retina	Reveal
Buys 1982	M64	LargeCell	Chor+Orbit	Reveal
Lakhanpal '82	F38	AdenoCa	Choroid	Reveal
Spaide 1989	M61	SmallCell	Orbit	no data
Ampil 1990	M61	SmallCell	Choroid	1 year
DeRivas 1991	M79	'Bronchus'	Iris +CB	Reveal
Sabbagh 1991	M47	SmallCell	Iris	Reveal
Duchamp 1992	M65	AdenoCa	Choroid	Reveal
Gaches 1995	F45	AdenoCa	Choroid	Reveal
Delemasure 95	M78	SmallCell	Iris	Reveal
Shields 1997	M55	Epiderm	Conjunct	Reveal
Veckeneer 1997	M73	AdenoCa	Choroid	Reveal
Gunduz 1998	M67	AdenoCa	Vitreous	8 mo
Rivière 1998	F56	SmallCell	Iris	7 mo
Ikeda 1998	F61	AdenoCa	Choroid	12 mo
Goto 1999	M67	SmallCell	Iris	7 mo
Latkany 2000	M76	AdenoCa	Vitreous	Reveal

(CB: ciliary body)

Metastases in the ocular muscles have rarely been described. Hehn et al. have reported on two cases, one from a small cell and one from a large cell cancer. In both it concerned a rectus muscle. This metastasis type is much less frequent in bronchial cancer than in other as breast or melanomas.

Gynecological Metastases

Metastases to the female genitalia from bronchial cancers have rarely been reported.

Reporting on a case involving metastases to the uterine cervix, Hollier found 7 other cases reported in the literature.

Ovarian metastases are probably underreported, as Young et al. were able to find only on seven cases. Three concerned small cell cancers, two large-cell, one adenocarcinoma and one was a bronchial carcinoid. They could retrieve a few debatable cases in the old literature. Volkes et al. have reported on a bronchial 'oat-cell' cancer metastatic to the ovary, one year after dia-gnosis of the primary, while Malviya et al. reported on a patient (F40) in whom the ovarian metastases were the presenting complaint and the bronchial cancer was found simultaneously at staging.

We found three case reports on placental metastases. We have added the cases retrieved by Read et al. (table 8.50). In none was the fetus involved.

Metastasis to the breast has been repeatedly reported, particularly in small-cell cancer (Three cases as first sign: Kelly et al. 2 cases; Hardwick one case; Sadikot et al.).

Table 8.50 - Cancer of the Bronchus
Placental Metastases reported

Barr 1953	??	Oat-cell
Hesketh 1962	??	Oat-cell
Jones1969	F39	Oat-cell
Read 1981	F37	Large cell
Suda 1986	F33	Large cell
Delerive 1989	F30	Oat-cell

Silverman et al. had 1 epidermoid, Chaignaud et al. 3 small-cell, Iwaszkiewicz 1 (NOS) and Domansky et al. one small and one large-cell in their respective series.

Excisional biopsy of a skin-invaded nodule in the breast in a F54 disclosed a mucin-positive clear cell adenocarcinoma. The same histology was obtained in the right middle bronchus and labeled a bronchial cancer. This was most probably an ectopic salivary gland tumor (Palgon et al.).

Metastasis to the Pituitary and Pineal Gland

Mentioned as the most frequent source of pituitary metastases in men, reports on series of this particular site from bronchial cancer are absent in the literature. Reviewing a few autopsy series, Bunn et al. found an incidence of 16% in small-cell bronchus patients.

We are aware of a few case reports with a particular

presentation. It will be noted that the majority (8/12) have involved female patients (table 8.51). Krol et al. mention that they have encountered three cases in 10 years.

Table 8. 51 - Cancer of the Bronchus
Metastases to the Pituitary Gland

Author	Pat	Histology	Symptom	Interval
Krol 1982	F54	Anaplast	Polydipsia	Reveal
Clavier 1987	F62	Small-cell	Polyuria	Simult
Markuse 1987	M62	Small-cell	Hypopituit	Reveal
Gernez 1991	M72	Small-cell	Asthenia(')	Reveal
Juneau 1992	F49	Carcinoma	Vision probl	Reveal
Jouanny '93	F81	Small-cell	Polydipsia	Simult
Jouanny '93	M62	Epiderm.	Polydipsia	8 mo
Ko 1994	F67	Adenoca	Polydipsia	Simult
Izumihara '95	M46	Small-cell	HeadA Polyd.	Reveal
Struk 1995	F47	Large-cell	HeadA Dipl	Autopsy
DeCanter '96	F50	Adenoca	Vision probl	Reveal
Lau 1998	F36	Bron.Alv.	Diplopia	Reveal
Metastases to the Pineal Gland				
Keyaki 1989	F70	Small-cell	Headache	Reveal
Kashiwagi '89	M66	Small-cell	Headache	Reveal

(') associated with hyperprolactinemia
HeadA : headache

One patient (M71) was reported by Noseda et al. as presenting with clear diabetes insipidus and symptoms of a bronchial tumor. It was confirmed as a small-cell cancer with several brain metastases, of which one at the hypothalamus, at the floor of the third ventricle.

Metastases to the pineal gland, a rare site indeed, have been reported in two patients (table 5.51).

Peripheral Arterial Tumor Emboli

As already mentioned in Chapter 7, peripheral arterial tumor emboli are a dramatic event in only a small number of bronchial cancers, but they are probably more frequent than generally accepted and responsible for many deaths in bronchial cancers, especially when the embol is located in cardiac and cerebral arteries (Whyte et al.). The embols can occur at all sites, and when large enough can be source of intense pain and will mislead many emergency doctors, especially when the bronchial cancer is unknown or the patient is unknown to the hospital. Starr et al. have stated that bronchogenic carcinoma may be the source of arterial tumor emboli in 38% of all cases.
A recent literature review (Xiromeritis et al.) retrieved 46 cases from primary lung cancer. A fatal case (M55) presenting with diffuse embols was recently reported, where at autopsy the diagnosis of a small cell lung cancer was made. Almost all pulmonary arteries showed foci of tumor emboli. The liver contained multiple metastases (Wong et al.).
We refer to Chapter 7, for further discussion on sites and symptomatology.

Other Metastases

Metastasis to the male breast has been reported by Silverman et al. in two cases from an oat-cell bronchial cancer. Another case was reported by Verger et al. from an adenocarcinoma of the bronchus, occur-ring 18 months after initial diagnosis.

A submandibular swelling in a 45 year old man turned out to be a first sign and metastasis of a small-cell cancer (Brodsky et al.).

INTRAVASCULAR BRONCHIOALVEOLAR TUMOR

Intravascular bronchiolo-alveolar tumor (IVBAT) is a rare pulmonary tumor first reported in 1975 by Dail et al. It is believed to have an endothelial origin. We have to include it in our discussion as several cases with distant metastases have been reported.

There is much discussion about the origin of the tumor. IVBAT is most probably a low-grade malignant epithelioid angiosarcoma, which may have a complicating distant metastases, mostly it is a misleading condition. Up to 1990, 37 cases have been reported (Carter et al.).
It is an idolent, generally non-aggressive tumor displacing pulmonary parenchyma over a number of years by slowly enlarging pulmonary nodules, mainly in the peripheral zone of both lungs. Some authors called it the pulmonary counterpart of epithelioid hemangioendothelioma.

Clinically it presents as bilateral pulmonary nodules with or without non-specific respiratory symptoms. It has an unusual clinical presentation as an anterior mediastinal mass, diffuse pleural thickening resembling malignant mesothelioma, a metastatic carcinoma with lymphatic spread, solitary calcified nodules and alveolar hemorrhage (Yi et al.).
Eighty percent of the cases are women and half are diagnosed before the age of 40.
Complaints are pleuritic chest pain (19%), cough (16%), dyspnea (13%), weight loss (7%) and shoulder pain (3%) (Ross et al.).

Metastases are uncommon but have been reported in the liver, in bone, in the bowel, the retroperitoneum and in the skin, sometimes as first manifestation, resulting in a difficult diagnostic problem unless the chest image is recognized (Miettinen et al.).
Only a few cases of low-grade malignant epithelioid hemangiosarcoma associated with bone tumor have been described. The rarity of the condition may lead to contradictory diagnose as the patient can consult either a pneumologist or an orthopedic surgeon, even a rheumatologist. Other authors (Verbeken et al.)

emphasize the fact that in bone hemangio-endothelioma, the lung pathology is metastatic and not a lung primary.

Metastases from MALIGNANT PLEURAL MESOTHELIOMA

Malignant pleural mesothelioma is a rare tumor. It is linked in more than three quarters of the cases with occupational exposure to asbestos and ensuing asbestosis. Pathologists have discerned three different forms, the epithelial, the sarcomatous and the biphasic type.
It is a tumor of the mesothelium and has some features of epithelial, adenocarcinomatous or sarcomatous nature.

The tumor is highly aggressive and invades neighbouring structures and organs. Distant metastases are rarely detected during patient's lifetime but frequently observed at autopsy.

The malignant pleural mesothelioma does not invade the lungs. It grows around the lungs' surface, encasing them, the heart and the great vessels causing progressive 'strangulation' leading to death.

Autopsy Data

Several small series have been reported. The largest is the series of Hartmann et al. on 106 patients (Table 8.52).

Table 8.52 - Pleural Mesothelioma
Distant Metastases (N=106)
Autopsy Data of Hartmann et al.

Infiltration		Distant Metastases	
Thoracic Wall	61.3%	Liver	22.6%
Diaphragm	48.1	Adrenals	14.1
Pericard	50.0	Kidney	9.4
Ipsilateral lung	20.8	Spleen	2.8
Lymph Nodes		Bone	18.9
Intrathoracic	47.1%	Brain	3.8
Extrathoracic	17.9	Gastrointestinal	2.8
		Peritoneum	32.1
Contralat.Lung	23.6	Thyroid	5.7
Contralat.Pleura	21.7	Myocard	7.5
		Other	7.5

As one can see from these data, intrathoracic spread as either wall infiltration or to the lymph nodes is the main status at death. As far as peritoneal metastases are concerned, it can either be truly contiguous spread through the diaphragm, though several cases have been reported where the overall mesothelium has become tumorous, similar to a field carcinogenesis.

Wadler et al. have reported on autopsy findings in 19 patients. Cardiac invasion was noted in 74%, with one third at multiple levels. Paricardial invasion was seen in 53%, with one patient having constrictive pericarditis. Myocardial involvement was seen in 26% and epicardial in 26%.

Thoracal Spread

Thoracal metastases can present as pleural effusion, pleural thickening, discrete or extensive pleural masses, large parenchymal nodules, hilar masses or rib destruction (Uri et al.). Moreover, bilateral parenchymal metastatic involvement has also been reported, although most reports do not separate hetero-lateral from ipsilateral metastases.
One singular aspect is that mesothelioma does not form tumor masses within the lung, nor is there any deep invasion within.
Consequently, there are good grounds for not considering the invasion of contralateral pleura as true metastases. A similar problem exists for contralateral lung, which can be invaded through the mediastinum.
The thoracal invasion can be very large indeed and unexpected large volumes, even protruding outwards through the intercostal spaces. An analogous problem is the invasion of spinal column in the thoracic zone. Some patients have been reported with destruction of the vertebrae with or without invasion of the spinal canal and vice-versa, causing paraplegia.
CT plays an important role in the detection and delineation the extent of the invasive spread (Table 8.53).

Table 8.53 - Pleural Mesothelioma
CT-features at Diagnosis N=50 - From data of Ng et al.

Pleural Features		Pulmonary Features	
Pleural thickening	94%	Atelectasis	74%
nodular	72%	Rounded atelectasis	9
uniform	28%	Bilat.lung nodules	7
less than 1cm	53%	Ipsilat. lung nodules	4
more than 1cm	47%	Volume alteration	
Super.Mediast.thick.	70%	None	63%
Diaphragma crura	84%	ipsilater.loss	27
Fissural involvement	84%	ipsilat med.shift	68
Pleural effusion	76%	enlargement	10
small	58%	ass.w. contralat.shift	5
1/3-2/3	26%		
more than 2/3	16%	Invasion of	
Pleural calcification	12%	extrathor. muscle	16
Pleural plaques	8%	Mediastinal Invasion	13
		Rib invasion	9
		Thorac.Ly.N. enlarg	34
		Involv.Diaphragm	80

There is some correlation between the metastatic pattern and the histology type (Fig 8.8).

Cardiac spread

Symptoms of cardial involvement may be present in 10% at presentation but in up to 60% of the patients at autopsy. Infiltration of the myocardium is less fre-

quent.
There was no firm correlation between level of tumor invasion and type of ECG abnormality in the 64 patients studied by Wadler et al., although only 11% had a normal study.
Walters et al. reported on a patient where the tumor had infiltrated through the atrial wall with large intracardial mass occluding the tricuspid orifice.

Sarcomatous and undifferentiated mesotheliomas have clearly more extensive local spread and more distant metastases. This is the case for liver, adrenals, kidney and most of the others, but also for contralateral lung and pleura. No metastases in the thyroid, the spleen, gastrointestinal tract have been seen in cases of epithelial mesotheliomas. This type has, however, more peritoneal and extrathoracal lymph nodes. Sarcomatous mesothelioma has more contralateral lung metastases and bone metastases.
The finding of Huncharek et al. are, however, at odds with this picture. They found in a series of 42 cases no differences in the incidence of metastatic disease between the three histological types (epithelial 75%, sarcomatous 70% and mixed 83%). The organ distribution was, however, not reported. Roberts had previously found no difference in metastatic incidence according to histology type in a small series of 32 autopsy cases.

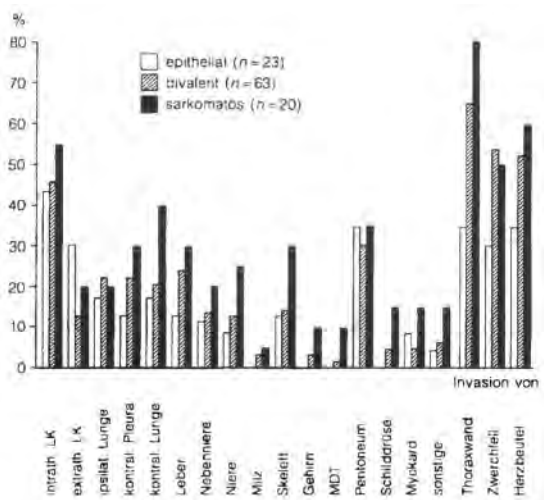

Fig 8.8 - Comparative incidence of infiltrative or metastatic lesions acccoring to the histology type (from Hartmann et al, with permission)

While CT has an important role in the delineation of the intrapleural and intrathoracal spread, together with pleuroscopy, Carretta et al. have recently reported interesting results with FDG-PET scan. It is claimed to play an important role in differential diagnosis with benign disease, but is apparently also able to detect mediastinal and other metastatic nodes not visible on CT.

Distant Metastases

While the most frequent 'true' metastatic site is the liver, we are aware of only one article concerning this site, and this describes a calcified metastasis in the liver.
As expected the more rare sites encountered in clinics are the subject of relatively more publications. Some sites are indeed very peculiar.

Head and Neck Metastases

Only 6 cases have been reported. In all there was extensive disease within the thorax and the metastases appeared during follow-up (Table 8.54).
In a review on pleural mesothelioma with intracranial metastases, Schwechheimer et al. found mention one case in 1891 involving metastasis to the orbit and sphenoid bone.

Table 8..54 - Pleural Mesothelioma Head and Neck Metastases Case reports

Author	Patient	Site of Metastasis
Edstrom 1980	M50	Sinus Maxillaris - Skin
Sproat 1993	M48	Mandibula, osteolysis
Kerpel 1993	M73	Tongue, ventral surface
Kerpel 1993	M45	Mandibula, osteolysis
Hefer 1997	M61	Tonsil Right
Piatelli 1999	M52	Tongue, lateral

Brain Metastases

Metastases to the brain are rare. Incidence data are derived from the data of large institutes.
An Italian study had 3 cases in a series of 171 patients, or 1.75%. Of all patients with metastases, it accounted for 3/93 or 3.2%. It is not clear if it concerned only the status at diagnosis (Falconieri et al.).
A much higher rate was reported by Brenner et al. At the Memorial Hospital (N.Y.), they noted 7 patients with brain metastases during follow-up of a group of 123, or 5.7%.
Reviewing the literature, Wronski et al. stressed the fact that of the 55 cases reported in 1993, only 15 were biopsy-proven, 32 mentioned either as clinical or at autopsy and 8 more unproven.
One noteworthy fact is that about three quarters had multiple sites within the brain, involving the hemispheres, the brainstem and the cerebellum. Extensive thoracal and/or abdominal spread was noted simultaneously in almost all cases.

Brain metastases are probably more common than is thought, though it must be kept in mind, as with other metastases, differential diagnosis with adenocarcinomas may be difficult.

In the areae of CNS-metastases, one report on leptomeningeal carcinomatosis (De Panger et al.) and two cases of extension and/or metastases within the spinal

canal (Cooper and O'Brien et al.) should be mentioned. These cases also had widespread metastases.

Extrathoracal Lymph Nodes

Cervical nodes have been reported in one patient as presenting sign (Wills), but more interesting are two cases reported with axillary nodes where the primaries of both patients were unknown (Craig et al. and Kim et al.). With reference to the above discussion in the chapter on systemic metastases, any adenocarcinoma within the axillary nodes with an unknown primary, should raise the possibility of a pleural mesothelioma.

Supraclavicular (Ansari et al.), axillary and inguinal metastatic lymph nodes have also been reported as revealing metastases from peritoneal mesothelioma (Sussman et al.).
Reviewing the literature in 1987, Kim et al. surveyed 401 reported cases, of whom 183 were autopsied. Axillary nodes were reported in only 2 patients, cervical nodes in 13 and abdominal nodes in 17. It should be remembered that axillary nodes are usually not sought for in the classic autopsy protocols.

Bone Metastases

Bone metastases constitute a particular problem. They must be differentiated from contiguous invasion from thoracal tumors.
One case of revealing metastases was reported by Taillandier et al. It was detected by a fortuitous iliac crest biopsy made because of a clinical picture of discrete anemia.
Other patients have been reported with multiple spine and/or pelvic metastases.
A patient (M56) presented with pain in the humerus and dull ache in the back. He had a far advanced mesothelioma and, at autopsy, the bone metastases were histologically confirmed (Laurini).

Other Metastases

Distant skin metastases over the abdomen, the cheek and the scalp have been reported
An erythematous eruption over the thoracic wall at some distance from a surgical scar was found to be metastatic mesothelioma and occurred one year after surgery and radiotherapy in a patient (M50) (Prieto et al.).

A mass infiltrating the muscles of the anterior compartment of the right forearm was at histology found to be the revealing metastasis of a right pleural mesothelioma in a man aged 38 (Laurini et al.).

Three cases with intracardial involvement either by a tumoral thrombus or a tumorhave been published.
El-Allaf et al. have reported two cases where the diagnosis was made after presentation with cardiac tamponade, one being a pericardial tumor.
Another patient has been reported where the diagnosis of metastases was made in a biopsy of colon polyp. At surgery, an extensive peritoneal metastatic status was found.

Kawai et al. reported on a case (M55) with several brain metastases where also both adrenals were involved. The involvement of the latter is also mentioned in a few other case reports.
Two cases with calcified liver metastases are claimed to have been reported. The hepatic calcification may be dystrophic within necrotic foci of metastasis (Campbell et al.). A solitary liver metastasis occurred 19 years after first presentation in a patient (F58) (Moretti et al.).
Greliner et al. have reported on a M52, where at autopsy, apart from metastases in the lungs, the thyroid, the peritoneum and several perpheral lymph nodes, multiple muscular metastases were also observed at all levels and all limbs. This is supposed to be the only mesothelioma case with muscular metastases that has been reported.

Overall Lesson

Pleural mesothelioma spreads mainly intrathoracally with destruction or compression of the lung without invading the lung nor the heart. These are the main causes of death. Distant metastases are somewhat uncommon and contribute relatively little to the mortality.

METASTASES from MALIGNANT THYMOMAS

Thymomas are rare tumors located in the anterior mediastinum. Different histology types are recognized. The classification is, however, intensively and lively discussed in the literature. This is beyond the scope of this chapter.
The metastatic rate depends on the stage of disease, but would appear to be relatively low after first treatment. Very long time intervals can occur. Only four series have dealt with data on metastases. The rate varies from 4 to 54% (Table 8.56).

Local and Distant Spread

Thymomas are commonly unilateral masses protruding into one hemithorax. They rarely extend into both. About one third of the thymomas are truly (histologically) invasive, growing through the capsule into the surrounding mediastinal fat and structures.
Local spread is characterized by an extensive contiguous invasion.
Within the virtual space of the mediastinum - the mediastinal fat - surrounding the thymus and the large vessels, a thymoma can progress in all directions.

Apart from invasion and filling of the space, it can actually invade all the vascular structures and anatomical structures as the pleura. Within the cavities as the pleura and the pericard, the thymoma can spread in the form of nodular implants or plaques all over. It can be considered a mass extending through all interfaces with a polycyclic extension.
The most frequent invasion is pleural invasion; invasion of the lungs, of the blood vessels, the pericard and the heart being less common. A few cases of invasion through the sternum have appeared in the literature.
Thymoma tumors can demonstrate dramatic invasiveness. Oldroyd et al. reported on a patient where the tumor penetrated through the sternum into the subcutaneous tissue. Nickels et al. reported on an extensive mediastinal spread of a thymoma with extradural expansion through the intervertebral discs and through the muscular diaphragm.
Bulging and/or invasion of the heart by an enlarging thymoma has been observed in a few cases (Gunn et al.). Invasion of the superior vena cava and the heart is not uncommon. Transdiaphragmatic growth into the abdomen and peritoneal cavities has been described.
Extension cranially in the neck as lymph node metastases has been reported even as first presentation (Barat et al.). The invasion out of the thymus capsule is an important staging limit and prognostic factor.

Distant Metastases

Although infrequent, distant metastases have been described in many organs.
Nodular metastases can be found throughout the lungs, the pleura and the liver. Osteolytic metastases in the bone are not uncommon, nor are brain metastases, who are usually solitary. Metastases can be the first sign of a silent thymoma.
Distant metastases are, of course, almost only found in patients with 'malignant' thymomas or thymic 'carcinomas' (Table 8.55).

When one reviews the case reports, the impression is gained that thymoma rarely have solitary metastases, but when present they are englobing large regions, in multiple organs, and with multiple nodules or superficial plaques.
In case of local progression, an important mediastinal mass can be present, with ramification towards the large vessels, exceptionally with invasion of the lumen with associated serious cardiac problems. This will be discussed later. Whatever structure is invaded it is always present in patients with 'malignant' thymoma. The data of Cohen et al. are very illustrative in that respect (Table 8.56).

Table 8.56 - Malignant Thymoma
Structures invaded as seen at surgery (N=23)
Data of Cohen et al.

Phrenic Nerve	8	Rec.Laryngeal Nerve	2
Major vessels	6	Lung	2
Pericard	6	Pretracheal fascia	1
Pleura	5	Mediastinal Node	1

Invasion of the large vessels has been found to be an important prognostic element (Okumura et al.).

Intrathoracic Metastases

As distinct from local invasion, distant metastases within the lung parenchyma, the pleura and the heart may occurr.
There are no reports specifically adressing the pulmo-

Table 8.55 - Malignant Thymoma
Frequency of Distant Metastases in some literature series.

	Cohen 1981 N = 23(+) Total 6 (26%)	Chahinian 1981 N = 11(') 6 (54%)	Maggi 1986 N = 169(+) (+) 7(4%)	Gorich 1988 N = 36 (") 11 (30%)
Thoracal				
Mediast.Nodes	--	--	--	5
Neck Nodes	--	2	--	4
Pleura(Extra Med)	1	--	3	6
Lung	1	--	3	7
Breast	--	--	1	--
Skin Thor.Wall	2	--	--	1
Abdominal				
Adrenals	1	--	--	3
Kidneys	1	--	--	--
Pancreas	1	--	--	--
Liver	3	1	--	2
Other				
Brain	1	--	--	1
Spinal canal	--	1	--	--
Bone	3	2	2	3

(') clinical series; (+) surgical follow-up; (") clinical series submitted to radiology

nary metastases. Rare cases have been reported where the pulmonary nodule was the first sign of a thymoma at last diagnosed at thoracotomy (Gilbert et al.). One other patient (F52) presented with signs of myasthenia gravis, but at chest radiography four discrete masses were seen in the left hemithorax, one in the anterior mediastinum, two other paraspinal masses and one at the cardia (McCrea et al.). This transdiaphragmatic extension will be discussed later in greater detail.

Metastatic lymph nodes in the mediastinum, with further spread towards supraclavicular and other neck nodes is seen. Lymphatic reflux through the diaphragm towards abdominal nodes has also been described in autopsy cases.

As expected, most cases which evolve in unfavorable ways will have either lung or/and pleural metastases, eventually with effusion (Zirkin). There will be, however, patients without thoracal involvement but widespread abdominal metastases.

Pleural involvement as first presentation has been reported in several cases. Moran et al. reported on 8 cases where the involvement was most plaque-like, but also only as a thickening or tumoro-nodular, with severe encasement of the lung. In that respect it can present as masquerading as pleural mesothelioma, illustrating the 'creeping' nature of the thymoma seeking its way through several planes, here probably below the pleural surface. A case like this was reported by Payne et al. in 1960 in M37 and more recently by Honma et al. in a 48 yr old woman.
Needless to say, CT plays an important role in delineation of the extension and invasion, a technique not at hand several decades ago for the older case reports.

Table 8.57 - Malignant Thymoma
Cases with endobronchial extension reported.

Author	Pat.	Involved Bronchus	Interval
Fournel 1985	M51	Ri.Inf.Bronch	7yrs
Fournel 1985	F52	Ri.Upper Lobe Br.	6yrs
Fournel 1985	M56	Le.Inf.Lobe Br.	Revealing
Honma 1988	F58	Left B3-bronchus	Revealing
Asamura 1988	F62	Ri.Main bronchus	Revealing
Asamura 1988	F56	Left B3-bronchus	Revealing
Kondo 1997	F68	Left B3-bronchus	Revealing

A few cases presenting with endobronchial polypoid growth have been reported (Table 8.57). The intrabronchial growth is always continuous with the mediastinal mass (Kondo et al.). The female preponderance and the invasion of B3-left bronchus should be noted.

Transdiaphragmatic Extension

The highly invasive nature of thymoma can be quite startling. The thymoma can extend towards the abdominal cavity and the retroperitoneal cavity. Three pathways may be involved.

1. The retrocrural space allows extension into the retroperitoneal space even up to the retrorenal space;
2. There are three small gaps in the anteromedial diaphragm; one midline and two parasagittal (foramina of Morgagni). As the endothoracic and transversalis fascia are a continuium, an extrapleural tumor under the endothoracic fascia can go through these small diaphragmatic defects, enter the anterior extraperitoneal space and find its way into the pararenal spaces;
3. A pleural or extrapleural (mediastinal) tumor can directly invade the diaphragm and enter the peritoneum, the peritoneal cavity or the extra-(retro-) peritoneal space and the liver surface. This will also allow spread to the chest and abdominal wall (Scatarige et al.) (fig.8.9).

From a series of 19 patients with proven invasive thymoma, the authors were able to detect transdiaphragmatic extension in six patients, or 31%. The sites included the lateral liver surface, posterior renal space, left para-aortic region, epigastric soft tissue and even the spinal canal. The presence of this extension should be scrutinized for on CT studies.

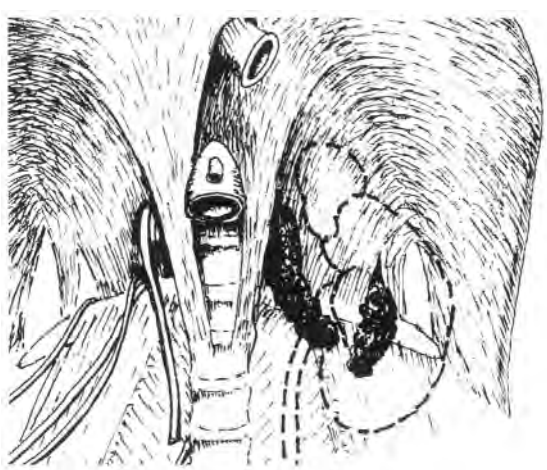

Fig.8.9 - Extension through the diaphragmatic crurae of a thymoma into the retroperitoneal space.

Metastases in the Central Nervous System

Involvement of the brain has rarely been reported. Rare cases involving the spinal cord, in the mode as seen by primary brain tumors have occurred (Wicks et al.). Diffuse enlargement of all cranial nerves, with leptomeningeal clouding over cerebral convexities at the base, the spinal cord, nerve roots and cauda equina, including sympathetic ganglia and dorsal roots have been described at autopsy. An overview of some reported cases is shown in table 8.58.

The case reported by Wagner et al. as involving a metastasis in the pituitary should most probably to be considered a bronchial carcinoma, as biopsies of the primary and pituitary metastases were both squamous cell carcinoma.

Table 8.58 - Malignant Thymoma
Reports on Metastasis in the Nervous System.

Author	Patient	Site of Metastasis
Lowenhaupt 1948	F27	Single cortical (°)
Rachmaninoff'64	F43	Le.Temporoparietal
Mottet 1964	M32	Ri.Parietal lobe (°)
Minkowitz 1968	F37	Le. Gyrus Hippocampus
Butterworth 1973	M36	Brain and spinal cord Meninges, Pituitary
MacDonald 1978	F14	Le.Occipital lobe
Jose 1980	F49	Left hemisphere (two)(')
Turpin 1984	M30	Le.Temporal (epilepsia)

(°) cited by MacDonald
(') also liver and nodes

Bone Metastases

Patients presenting only with bone metastases are very rare. One case with an extensive osteosclerotic and lytic process in the upper epiphysis of the femur was reported by Scalley et al..
Various metastatic sites have been seen at bone scintigraphy as in the hip, the shoulder and both femora (Cancroft et al.).
Another case involved a solitary metastasis in Th-4 with spinal cord compression, occurring 1 year after diagnosis of a mediastinal thymoma confirmed by FNAB and treated by chemotherapy. This may be considered as a contiguous invasion from the mediastinal tumor towards the vertebra, as far as the description of the case permits.
In a patient with widespread metastases, Minkowsky found metastasis in a lumbar vertebrae. Several vertebral metastases were seen in one case reported by Turpin et al., together with one brain metastasis.
Two cases have been reported where among other metastases, an osteolytic mass was seen at the sternum, both in continuity with the mediastinal mass (Butterworth et al.; Oldroyd et al.).
Recently, Shannon et al. reported on a M54 who presented with a swelling at the right ring finger seven years after surgery for a poorly differentiated thymic carcinoma. He was found to also have a cerebellar and multiple pleuropulmonal metastases.

Abdominal Metastases

In several case reports, metastases all over the peritoneal serosa of the stomach, the small intestine, the colon, but also with abdominal, pelvic, periaortic and peripancreatic nodes have been dsecribed. Some present also with pelvic masses, as well as hilar and perirenal masses. In a case reported by Turpin et al. there were also ovarian metastases. In all these patients, a number of liver metastases are present. A patient with a very extensive abdominal spread, including ovary, mesentery, distal colon, bladder and pelvic cavity was recently reported by Bott-Kothari et al. The first indication of metastasis occurred 6 years after first treatment of a Masaoka stage IVA thymoma.
Some cases with solitary renal metastases have been reported (Table 8.59). One patient with a large pararenal mass and hematuria was reported by Reddy et al.. They also reported on a patient (M72) presenting with a large abdominal mass causing bile duct obstruction and confirmed at FNAB.

Table 8.59 - Malignant Thymoma
Reported Renal Metastases

Hietala 1977	M25	hematuria	Ri.kidney
Needles 1981	F19	hematuria	Ri.kidney

Cardiac Problems

Contiguous invasion of the pericard is common. This can result in pericardial nodules, later possibly expanding to masses with or without pericard effusion (Table 8.60). The presenting cases always had a usually large mediastinal tumor encroaching on the pericard and sometimes invading the heart. This must be differentiated from the very rare primary pericardial thymomas.

The case (F66) reported by Ando must be regarded a primary located or at least very close to the pericard. Malignant epidermoid cells from the pericardial effusion more suggestive of a bronchial cancer, but autopsy finally revealed the thymic primary.

Table 8.60 - Malignant Thymoma
Cases with Pericardial Effusion

Author	Pat	Sign	Presentation
Canedo 1977	M17	Incidental finding	
Venegas '88	M30	Effusion	Revealing
Chow 1992	M76	Effus.+Mass	Revealing
Woldow '95	F70	Effusion	Revealing
Ando 1995	F66	Effusion	Revealing

True myocardial metastases have been described in some case reports at autopsy.
The most frequently reported problem is invasion of the superior vena cava, with a tumor thrombus extending to within the right atrium and on rare occasions protuding through the triscuspid valve. The symptomatology is that of ventricular inflow or outflow obstruction (see chapter 1).
Rare cases have been reported, mainly in the Japanese literature (Table 8.61).

Table 8.61 - Malignant Thymoma
Intracardiac Invasion with flow obstruction
Cases Reported

Author	Pat	Site	Interval
Airan 1990	M38	Cava+RA+RV	Presentation
Yokoi 1992	M72	Cava+RA	Presentation
Massault 1992	F65	Cava+RA+Va	Presentation
Futami 1993	M56	Cava+RA	Presentation
Okereke 1994	M25	Cava+RA	Presentation
Filippone '97	F52	Cava+RA	Presentation
Minato 1999	M44	Cava+RA	Presentation
Hayashi 2000	M72	Cava+RA+RV	3years

A massive thymoma in front of the aorta, the pulmonary artery and the right ventricle with invasion of the pericardial sac anteriorly was responsible for respiratory distress in a 55 year old woman (Nishimura et al.).

Liver Metastases

Metastases to the liver from thymomas are not frequent. They can result from transdiaphragmatic extension as discussed above, but most are hematogenic. A few cases have been reported.
An isolated hepatic metastasis in the right lobe was recognized in a patient (F62) twenty-two years after treatment for an invasive thymoma (DeNayer et al.).

Other Metastases

Hoeffel et al. have reported on a patient (F32) presenting with jaundice seven months after surgery for a mediastinal thymoma. An exploratory laparotomy confirmed the metastatic nature of the tumor in the pancreatic head.
A splenic 'tumor' excised because of hypochondrial pain was not recognized as a metastasis of a thymoma until the thymoma was 'discovered' five years later (Ibrahim et al.).
Bilateral solitary breast metastases occurred within a month of mediastinal surgery in a F42, confirmed at FNAC. A breast metastasis was reported at autopsy in the patient of Minkowitz et al., together with several other metastases.
Stockl et al. reported on a thymoma with metastases in the orbit. We suspect that this case concerned a small cell cancer of the lung.

METASTASES from TUMORS of the HEART

Tumors of the heart are rare. The most common are benign myxomas, while malignant tumors of the heart, mainly sarcomas, are much rarer.
In spite of obvious benignity, a kind of metastatic behavior has been observed in some cardiac myxomas.

Cardiac Myxomas

Metastatic and/or myxoma-aneurysms constitute a topic of discussion in the literature, as is the regrowth of tumor in new locations, and whether they are metastasis or an embolus indicating the possibility of malignant biological behavior of cardiac myxoma. The development of mycotic aneurysms as a result of infiltration of the arterial wall by myxoma cells may support this. Histological studies of these emboli may demonstrate amphophilic myxoid material with pleomorphic giant cells (Horn et al.). De Sousa et al. have suggested an extensive classification for the metastases. Recently, Mattle et al. stated that myxoma metastases sometimes remain within the vessels and sometimes invade and transgress the arterial wall. It would appear that both lesions can occur. Angiography may show occlusions of cerebral vessels or aneurysm.

Two causes of cerebral aneurysm formation due to cardiac myxoma have been suggested (Furuya).

1. Stoane proposed the theory of vascular damage, by large tumoral emboli causing perivascular damage with scarring, followed by formation of pseudoaneurysm after obstruction.
2. Burton and later New et al. have suggested that the tumor embols remain viable and penetrate the endothelium at the site of final lodgment, giving rise to a subintimal growth, destruction of the wall and a proliferation.

Many available case reports describe an embolic event involving brain, spleen, kidney, finger but also coronary, iliac and mesenteric vessels leading to the diagnosis of a myxoma (Diflo et al.).
Recently, Horn et al. reported on a 42 yr old man in whom the diagnosis of a left atrial myxoma was made after excision of an aortic trombus, demonstrating myxoma features on histology. No other such case has been reported to date.
On the other hand, only a few reports mention a 'metastatic' proces diagnosed many years after the curative resection of the myxoma. They were localized in the brain, occurring as a lytic lesion in the pubis, as a mass in the sternum, as a tumor in the forearm and in the right leg (Diflo et al.). A large lytic biopsy-proven lesion in the humerus occurred in a 18year old female nearly 3 years after resection (Markel et al.).

Malignant Cardiac Sarcomas

There are no statistics on the incidence of distant metastases from cardiac sarcomas, as they are very rare. It is evident that tumors, which can shed cells within the right cardial cavity will bring the risk of first metastasizing in the lung, while those located at the left cavities will give rise to metastases anywhere within the body first; for example in the brain or the liver. When the tumor is located more at the outside of the cardiac wall, they will invade the mediastinum or shed cells in the lymphatics.
We have collected 294 case reports from the literature and noted the metastases when described.
As can be expected pulmonary metastases are much more frequent for right-sided tumors than for left-sided (table 8.62).

Table 8.62 - Sarcomas of the Heart
Pulmonary Metastases
Authors' review

Right-Sided	158	23%
Left-Sided	110	8%
Angiosarcomas	105	32%

As angiosarcomas are the most frequent, better data are available for this group of tumors (Table 8.63).

Table 8.63 - Cardiac Angiosarcomas
Metastatic rates in some reported series or reviews

Glancy 1968	41	27 or 66%
Janigan 1986	46	33 or 72%
Herrman 1992	35	24 or 69%
Butany 2000	67	30 or 45%
ante-mortem :		13 or 19%
in follow-up:		17 or 25%

A detailed review of the cases of cardiac angiosarcomas reported up to 1993 was done by Rettmar et al. It highlights the fact that the majority of patients have multiple metastases and that common sites of metastases such as lung, liver and brain are the most frequent. After all, it concerns a muscle sarcoma 'born' at the center and cross-roads of large vessels (Table 8.64).

Table 8.64 - Cardiac Angiosarcomas
Distant Metastases at Autopsy (N=98)
Literature Review (Rettmar et al. 1993)

Autopsy Complete	43/98		
No Metastases	5/43 (11.6%)		
Single Metastasis	6/43 (lung 4x, pleura,CNS)		
Multiple Metastases	32/43 (74.4%)		
Lungs	51.2%	Liver	37.2%
Pleura	20.9	Spleen	20.9
Lymph Nodes	16.3	Kidneys	11.6
		Adrenal	9.3
CNS	30.2	Ovaries	9.3
Bone	20.9	Peritoneum	7.0
Skin	7.0	GI-tract	7.0
Muscle	2.3	Pancreas	7.0

Table 8.65 - Cardiac Angiosarcomas
Distant metastases (Review by Butany et al. 2000)

Site	At Diagnosis N=13/67	After Surgery N=17/67
Lung	10	4
Brain	0	6
Bone	3	1
Colon	1	0
Not specified	3	6
Total	17	17

These data show the high rate of distant metastases, at last for this histological type. As most angiosarcomas are at the right, lung metastases are frequent, but further distant metastase are not uncommon (Table 8.65). The pericard is involved in about 60% due to contiguous invasion. Compared with earlier reports the diagnosis of heart sarcomas is easier to make, as well as the diagnosis of metastases. Surgery has been incriminated causing more brain metastases. It is, however, probable that natural further evolution is responsible, and not surgery, at all.

Quite a number of cardiac tumors have presented with metastasis first. Needless to say, such a diagnosis needs some awareness. We have grouped some cases in Table 8.66, but we do not claim completeness. The high diversity of the metastatic locations is surprising. The metastasis in the thyroid, the pancreas and several in the cerebellum should be noted.

Table 8.66 -Cardiac Sarcomas
Tumors Revealed through Distant Metastases
From the available literature

Author	Pat	Histology	Site of M
Coulter 1961	M25	Fibrosarcoma MV	Brain
Depierre 1961	F29	FibrosarcomaRA	Mult.Pulmo
Glancy 1968	F35	AngiosarcomaRA	Cerebell. (2x)
Herhusky 1985	F15	Fibrosarcoma RA	Pleural mass
Herhusky 1985	F35	Pleom.Sarc LA	Bone Le.Hip
Freed 1986	M23	Angiosarc RA(°)	Cerebell.Bone
Yousem 1986	F28	Angiosarc. RA-RV	PleuroPulm.
Bic 1994	M43	Angiosarc RA RV	Mult.Pulmo
Haugen 1994	F44	Mal.Fibr.Hist. LA	Thyroid
Maruki 1994	F44	Mal.Fibr.Hist. LA	Mult.Brain
Makhoul 1995	M64	Angiosarcoma RA	Bone L1-4(°)
Pomper 1998	M43	Angiosarcoma RA	Skin on face
Jahns 1998	F66	Osteosarcoma LA	Embols mult.
Baham 1999	M29	Angiosarcoma RA	Mult.Pulmo
Khalbuss 1999	F74	Rhabdomyosarc LA	Pancreas (°)

(°) the metastasis presented together with cardiac symptoms

The literature on heart sarcomas is very dispersed and some case reports are quite unclear.

We have retrieved some additional peculiar metastatic sites as far as mentioned in the reports.

Angiosarcoma : metastases to the stomach, urinary bladder, small and large intestine, uterus, bone marrow

Osteosarcoma: thyroid, skin

Fibrosarcoma : muscle of the thigh.

The overall lesson is the ubiquity of metastases from a cardiac sarcoma, with a relative high number of first presentation, resulting in a pitfall misleading the most alert clinician.

METASTASES from CANCER of the MALE BREAST

Breast cancer in males is a rare disease. Because of its low incidence, there are few data on metastases, in spite of the fact that 20 to 40% of the patients have metastases at presentation. Even in large series is the presence of metastases hardly discussed. There are also no autopsy series nor data on metastases. Although several hundreds of articles have discussed this cancer site, only very few give some 'raw' data on the location of metastases. We have grouped them together in the table 8.67.

The lungs and bones are the most frequent sites for metastases. There are no reports on pattern of skeletal metastases. Pleural metastases are also frequently reported. However, there is a very clear under-reporting of metastases for this cancer (table 8.68).

Table 8.67 - Male breast cancer - Site of distant metastases (literature data)

Author	Treeves	Greening	Walach	Scheike	Yap	Erlichman	Hodson
Year	1959	1965	1974	1975	1979	1984	1985
Number	N=42	N=28	N=42	N=257	N=87	N=89 (')	N=50
	Lung 8	Lung 9	Lung 12	Lung 64	Lung 31	Lung 14	Lung 8
	Bone 23	Bone 9	Bone 9	Bone 69	Bone 31	Bone 27	Bone 6
			Liver 3	Liver 23	Liver 14	Liver 0	Liver 2
			Brain 1	Brain 5	CNS 5	Brain 3	
	Skin 6					Skin 18	
	Ax.Nodes 9	Ax.No 4				Nodal 8	
		Su.Cl.No 3					Chest wall 10
	Soft parts 2	Other B. 1			Pleura 26	Pleura 15	Pleura 7
	No M 4				Other 3		

(') sites of recurrences; B: breast; No: nodes.

Table 8.68 - Male breast cancer
Summary of unusual sites of metastases

		Site	Interval	Other Metastases
Keeley 1973	M67	Bilateral patella metastases (as first sign of widespread)	4 years	Multiple other
Schlaen 1986	M58	Blurred vision- proptosis Orbital and choroidal Metastasis	11 years	Lung metastases
Choukas 1993	M43	Mandibula (as first sign of widespread)	8 years	Multiple other
d'Abrigeon 1994	M75	Stomach	4 years	No other site
Kim 1998	M62	Extensive skin abdomen, groin, lower extremity		Multiple other

METASTASES from CANCER of the FEMALE BREAST

The ubiquity nature of metastases from female breast cancer is well known. The frequency and time sequences of metastases in every organ is not known with a great degree of accuracy.
A number of studies have evaluated the relative frequency in the different organs or systems. Congruent data have been obtained in autopsy studies, although for some organs the results are highly dependent on the diligence of the pathologist performing the section and the pattern of microscopic study done. Time sequence and frequency during follow-up is almost never addressed.

After diagnosis and even after the adequate treatment of a localized breast cancer, more than 60% of these patients will later develop metastatic disease.

The clinical picture, the complaints and the clinical symptoms announcing a metastatic disease, has a large diversity.
While metastatic localisation in bone, lungs and liver by far outnumbers the other anatomic sites, their clinical manifestation is variable, although many symptoms and complaints are stereotypical and pathognomonic.
When a metastatic disease occurs in other sites - and for breast cancer it can be almost everywhere - the clinical symptoms are still very variable. This mwill mean that correct diagnosis will be difficult. Indeed, almost all complaints can also be caused by a wide variety of other pathologies, even other primary tumors.

In spite of vast data now accumulated in the different on-going trials, it is remarkable how difficult it is to find good data in the literature. It would be interesting that they should now release data on the type of metastasis and time-lapse during their now rather year long follow-up.

Loco Regional Evolution

Much has been written about local intra-mammary spread with its tendency to invade the entire breast, the skin and the thoracic wall. We will limit the discussion to tumoral progression and the local lymphatic spread.

Lymphatic spread (fig. 8.10) extends to the regional lymph nodes, such as the internal thoracic (mammaria inter-na), the axillary and its prolongement towards the supra-clavicular nodes, though the latter is no longer considered a node but a distant metastasis in the UICC-TNM nomenclature. The UICC nomenclature is a purely clinical one, no longer considered of any practical prognostic value (table 8.69).

Table 8. 69 - Breast Cancer
UICC Rules for Staging Nodes

N0	No palpable homolateral axillary lymph nodes
N1	Movable homolateral axillary lymph nodes
	N1a : not considered to contain growth
	N1b : considered to contain growth
N2	Homolateral axillary lymph nodes fixed to one another
	or: fixed to other structures, and considered to contain growth
N3	Homolateral supraclavicular or infraclavicular lymph nodes considered to contain growth

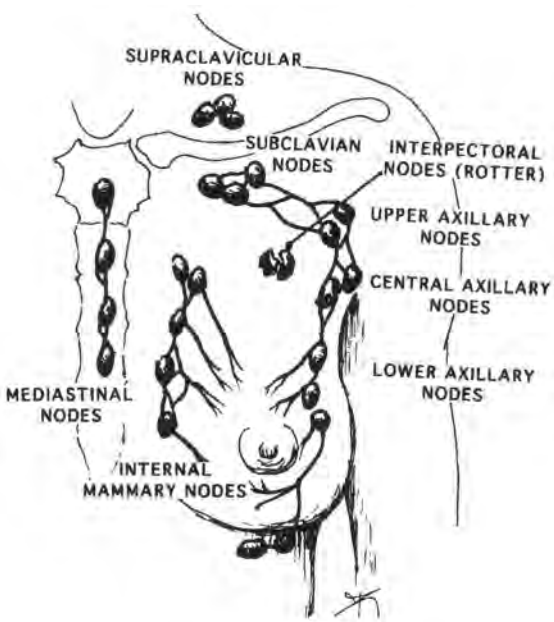

Fig.8.10 - The different regional lymph nodes of the breast.

Lymph Drainage from the Breast

A superficial system in relation to the skin exists, including a subepithelial or papillary plexus and communicating with subdermal and subcutaneous lymphatics. They are very important in the cutaneous and subcutaneous spread of the carcinoma. They communicate with deeper intramammary and perilobular lymphatic vessels along the lactiferous ducts and several connections between dermis and periglandular tissues (Canavese et al.).
The major part of the breast is drained to the axillary node, a group of 8 to 36 nodes. Rouvière has divided them into 6 groups (Sacré).

1. the external mammary nodes, close to the lateral thoracic artery at the height of the digitations of the m.serrate anterior;
2. Scapular nodes following the thoracodorsal branches of the subscapular vessels. The group contains 5 to 6 nodes;
3. The central nodes along the axillary veins or the most important group. They are embedded in the axillary fat, lateral from the lateral border of the musc. pectoralis maior. They are easily palpable in the axilla;
4. Nodes along the axillary vein or the subclavicular nodes. They extend from the origin of the vena thora-coacromialis up to the apex of the axilla;
6. The interpectoralis nodes are located in low number between both pectoralis muscles.

Axillary Lymph Nodes

For clinical and surgical purposes, the different central axillary nodes are divided into three levels (fig.8.11). Level I or the lower are defined as those along the chest wall and the lateral portion of the axillary vein. Level II is located behind the m. pectoralis minor and along the lateral half of the axillary vein, while level III is located medial to the m. pectoralis minor up to the thoracic outlet (Pigott et al.).
There is an extensive literature on several aspects of the implications of metastatic axillary nodes. The data and discussion are almost always centered on the diagnosis and the impact on the prognosis and treatment.

Data on the involvement according to several clinical or pathological features are however not frequently reported.The involvement will increase with size of the primary (table 8.70).

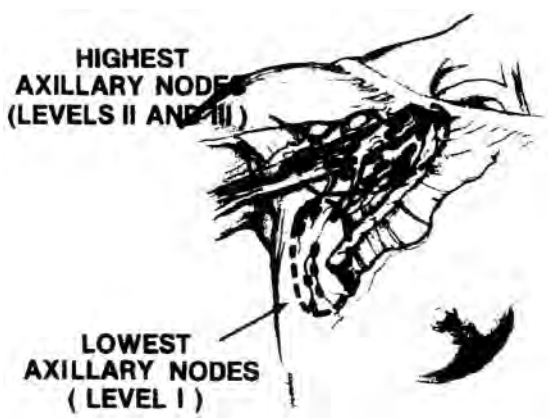

Fig.8.11 - The anatomy of the sublevels of the axillary nodes (from Pigott et al., with permission)

Table 8. 70 - Breast Cancer
Axillary Node Involvement and Size of Primary

Size	Foster Percent		Pandelidis (N=455)
<0.5cm (T1a)	17%		3.7%
0.5-0.9 (T1b)	20		11.7
1.0-1.9 (T1c)	39		20.0
2.0-2.9	41	>2 cm	32.1
3.0-3.9	49		
4.0-4.9	58		
5.9-9.9	66		
10.0-	71		

Table 8. 71 - Breast Cancer
Axillary Node Involvement and Size of Primary
Data of Shetty et al.

Size	Patients	N+	N: Nodes	N:Nodes+
0.1-0.5	51	7.8%	765	0.5%
0.6-1.0	208	16.3	3126	3.2
1.1-1.5	273	23.0	3823	5.8
1.6-2.0	226	35.8	3307	8.3
2.1-2.5	175	45.7	2996	12.0
2.6-3.0	91	44.0	1370	10.4
3.1-3.5	69	55.0	1244	14.8
3.6-4.0	45	64.4	789	26.1
4.1-4.5	28	60.7	434	27.9
4.6-5.0	28	64.3	420	37.9
5.1-10.0	47	74.5	948	32.2
>10cm	3	100	43	55.8

For tumors of less than 4 cm, 60% of the patients will have positive nodes, but only 25% of the resected nodes have been invaded (table 8.71). The site of the primary has some influence as the outer sites have a somewhat higher involvement, but this does not seem significant (table 8.73).

With an average number of 6.4 involved nodes per patient, in half of them the first level will be invaded. With increasing T-stage, the further levels will be increasingly involved. The number of positive nodes correlates with T-size or stage (table 8.72), but one should note that the involvement of a single node is sufficient to call the patient 'node-positive'.

Reviewing the literature on small cancers (below 1 cm), Morrow observed an incidence of 17 to 26% in sizes below 1 cm, but 3 to 28% for a size smaller than 0.5 cm, probably not significantly different. Nevertheless, the conclusion was that 1 patient in 4 with a such small sized tumor has positive (1 or more) axillary nodes. Similar figures were recently published in 4771 patients by Axelsson et al. For intraductal or in-situ, the literature data vary between 0 to 4.0%. Somewhat similar data were retrieved by Recht et al.

Table 8. 72 - Breast Cancer
Involved Number of Axillary Node and Tumor Size
Data of Veronesi et al.

Number	T1	T2 <2cm	T3 2-5cm	Total >5cm
	N=831	N=565	N=50	N=1446
0	51.1%	30.3%	22.0%	42.0%
1	16.6	12.7	10.0	14.9
2-3	13.7	17.2	8.0	14.9
4-10	11.4	20.2	22.0	15.2
>10	7.1	19.6	38.0	13.0

Data on the incidence of axillary node involvement according to the axillary level have been provided (among others) by Veronesi et al. (table 8.74, fig. 8.12) and by Pigott et al. The latter, reviewing the data of 146 patients, of whom 80% had positive nodes in the axilla, found involvement of 72% at level I, 78% at level II and 43% at level III. They observed the fact that in 25% the involvement was confined to level III, indicating a non-orderly involvement of the axillary group. However, they did not correlate the data with the site of the tumor within the breast.

Table 8.73 - Breast Cancer
Axillary Node Involvement according to Location
Data of Pandelidis et al.

Site	N	Axill. Involved
Nipple -Central	28	14.2%
Upper Inner	60	11.7
Lower Inner	32	9.3
Upper Outer	269	16.7
Lower Outer	36	13.9
Overlapping	34	14.7
Not specified	17	5.8

Table 8. 74 - Breast Cancer
Axillary Node Involvement by Level
Data of Veronesi et al.

Level	T1	T2	T3	All
	N=406	N=394	N=39	N=839
I	64.8%	46.2%	25.6%	54.2%
I+II	16.7	27.1	30.8	22.3
I+II+III	16.5	25.9	43.6	22.2
Skip	2.0	0.8	--	1.3

Histology is a difficult problem since different subtypes have been recognized. It is generally accepted however that to the two most frequent types, the ductal (90% of all) and the lobular type (9%), and the rare tubular cancer (1%) can be added. We found data on the relation between histology and axillary positivity in a report by Leonard et al. (table 8.75), but a clear difference between the two most frequent types has not been made.

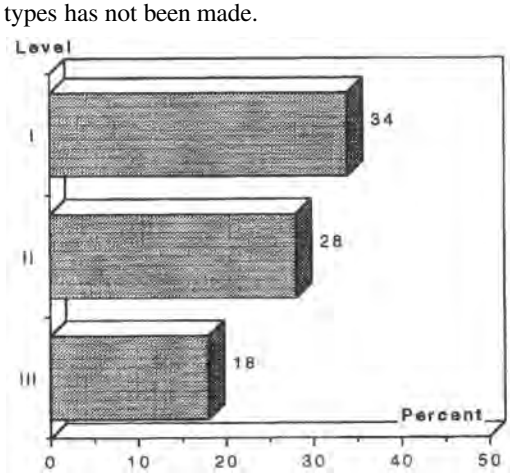

Fig.8.12 - Nodal involvement at each level of axillary nodes (N=839 patients), drawn from data of Veronesi et al.

As we discussed in Chapter 7, patients can present with axillary nodes first, without any clinically obvious breast tumor. In female patients, there will indeed be a strong probability that a small 'occult' breast cancer is the cause, but other primaries should not be excluded.

Table 8.75 - Breast Cancer
Axillary Node Involvement and Histology
Data of Leonard et al.

Histology	N	Axillary Involvement T <2cm	T>2cm
Ductal	14328	27%	59%
Lobular	1182	25%	58%
Tubular	209	12%	5%

Reporting on 42 patients, Ellerbroek et al. observed that mastectomy could detect only 1 cancer in 13 patients and a biopsy only in 1 in 5 patients. During follow-up of the 29 patients who did not undergo mastectomy, a tumor was observed in 17% of the patients who had been irradiated, but in 57% of those who had not been irradiated. One can asume that it concerned intra-ductal cancers, although they have a low incidence of axillary nodes. Further follow-up may well have disclosed other cancers, possibly non-breast cancers, but data are not given.

One unusual aspect is the occurrence of heterolateral axillary metastatic nodes. At presentation or during follow-up, they are likely to be seen in about 5%, according to Daoud et al. In a few patients no other metastatic site was observed. The occurrence can be explained as a lymphatic spread along the mediastinal and/or thoracic (intercostal) wall.

Any relationship between axillary node positivity and distant metastases is difficult to find in the literature. It is well known, however, that while both ways of spread are independent, the presence and outgrowth of nodal metastases will certainly constitute a further source of distant metastases. Data from Stockholm indicate a higher incidence of distant metastases in node-positive patients (table 8.76).

Table 8. 76 - Breast Cancer
Positive Axillary Node and Distant Metastases
Data of Rutqvist -Strom

	at 10 year LocoRegional	Rec.	Distant M.
Node Negative	after Surgery	23%	
	after Surg.+RT	5%	
Node Positive	after Surgery	55%	65%
	after Surg.+RT	21%	48%

Table 8.77 - Breast Cancer
Positive Axillary Node and Distant Metastases
Data of Strom et al.

N of Positive nodes	N of patients	Distant Metastases
1 to 3	310	17%
4 to 7	181	21
>7	136	47

Nodes at the Mammaria Interna Vessels

In each parasternal zone behind the costal grid, the internal mammary chain lies along the internal mammary vein and artery, from the first to the sixth intercostal space (fig.8.13). They are probably the first intra-thoracal nodes involved when malignant cells travel towards the mediastinum.

The incidence of involvement has not been studied as extensively as the axillary, but there is general agreement that it is higher for tumors at the inner side of the breast. Extensive data have been reported by Cody et al. (table 8.78). The data on fig.8.14 show that the most frequently involved node is at the second intercostal level.

Fig.8.13 - The nodes along the mammarian vessels, seen from behind (from Rubin et al., with permission)

Nodes at this site can grow to large dimensions pushing through the intercostal space and becoming visible at the thoracal surface (fig.8.14).

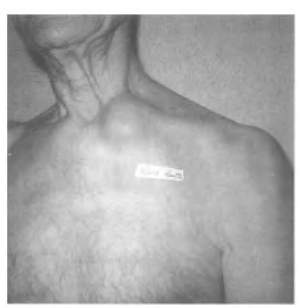

Fig.8.14 - Patient presenting with outgrow of a node at the mammaria interna through the intercostal space. Author's collection

Data according to the site of the primary have been reviewed by Foster. Adding 12 reported series totalling more than 4,000 patients, they obtained the following data, indicating a three times higher involvement in cases located at the inner half compared with those located at the outer half.

Medial Primary N= 2,258 : 7.3% (4.8-25.9%)
Lateral Primary N= 2,314 : 2.9% (1.6-4.1%)

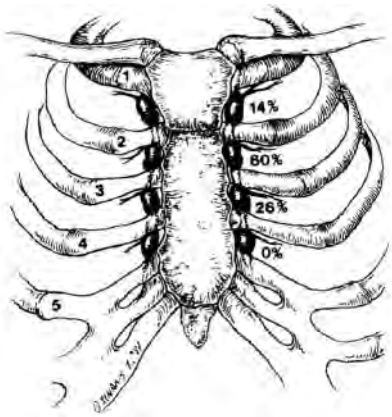

Fig.8.15 - The location of the internal mammary nodes related to the intercostal spaces and the incidence of involvement (from Scatarige et al., with permission)

Table 8.78 - Breast Cancer
Features of Mammaria Interna Involvement
Data of Cody et al.

Size of Tu		Axillary Status	
0-1 cm	36%	+ at level I	34%
1-2	24	+ at level II	35
2-3	19	+ at level III	47
3-4	40	negative	18%
4-5	30		
>5	33	Age of patients	
		<40 yrs	35%
		41-60	24
		>60 yrs	20

Semiglazow has published data on 608 patients submitted to extended mastectomy. The data show that one quarter of the patients were node-negative at both sites, but that in 12% the mammary nodes were positive in 12% without positive axilla.
Other interesting data were reported by Koscielny et al. They observed that in tumors situated at the inner half, the involvement of any group is associated with more involvement in the other group (table 8.79).

Table 8. 79 - Breast Cancer
Tumors Located at the Inner Half
Involvement of the Lymph Node Regions

Number of Axill.Involved	Mammaria Interna Nodes Not Involved	Involved
None	31.7%	8.8%
1-3	35.9	30.4
4-7	18.3	26.3
>7	14.1	34.5

Supraclavicular Lymph Node Metastases

The supraclavicular nodes have received much less attention in the literature because they are somewhat out of reach of the classic surgery of the breast. Nevertheless, nodes in the supraclavicular region are not uncommon during the evolution of breast cancer. They are almost always a sign of progressive disease from the axillary region out along the subclavian chain. They are just as ominous as any other metastasis. They seldom derive from a progression of mediastinal involvement.
When they become somewhat larger, they can invade the nervous plexus, hereby causing brachialgias. Compression of the axillary vein through outgrowth and invasion of the lymphatics can result, with edema of the arm.
In an oncology practice, supraclavicular nodes (SCN) are not uncommon. According to Cervin et al., 17% of them are from breast cancer. Another 22% are from pelvi-abdominal tumors and the majority (31%) from bronchial tumors.
As far back as 1940, Haagensen and Stout recognized that clinically evident SC-nodal disease carried a poor prognosis. This became one of their criteria of inoperability, which according to Strom et al. has resulted in a low number of data relating clinical parameters with the probability of pathological involvement of SC nodes. These metastases are usually grouped together as 'loco-regional' with the nodes in the axillary region when the number of regional lymph node metastases or recurrences are discussed. Supraclavicular node metastases (SCN) are, except for a few reports, relatively infrequently and only briefly discussed.

The axillary and SCN are in fact one single 'subclavian' chain, the SCN being its medial part (MacWirther). Malignant cells from a breast cancer can reach the SC zone along the subclavian chain resting on the top of the lung, via the axillary nodes or through the internal mammary chain situated along the internal mammary artery situated retro- and parasternally. It is estimated that 75% of the cells reaching the SCN pass through the axillary nodes.
When a SC-node is found, it should be assessed for presence or absence of malignancy by a fine needle aspiration. For cytology, a sensitivity rate of 98% and a specificity rate of 100% has been reported (Ciatto et al.). Imaging methods as CT or MRI can certainly demonstrate these nodes and will may even show more nodes in adjacent non-palpable regions.

Incidence

Reviewing the literature in 1966, Jackson found a mean of 15% (from 8 to 24%) at presentation. Halsted himself quoted 18.5% at presentation (table 8.80). He performed supraclavicular dissection in 119 patients and found 44 (37%) with involvement of the nodes.
Stage limits were only agreed upon just before 1940, and it is not improbable that in these early series a large proportion of the patients had tumours that would be categorized presently as T3- (T4) type.
Boyd et al. reported on 679 'technically operable' patients on whom a radical mastectomy was performed. This retrospective study mentions 61 (9%) patients presenting with a SCN. In the next 5 years a SCN occurred in 85 patients (12.5%), not comprizing 17 other patients in whom a cervical node presented.

Table 8. 80 - Breast Cancer
Incidence of SCN at first presentation
Review by the author

Author	N	N.SCM	%.SCM
Halsted	236	44	18.5%
Dalbet	24	5	21
Margottini	75	18	24
Andreasen	98	17	17
Dahl-Iversen	268	21	8
Boyd	679(')	61	9
Papaioannou	60(°)	15	25(")
Kiricuta	795(')	20	2.6
Perez (*)	281	36	13

(°) only stages III and IV
(') only 'operable' cases.
(") 50% when pathology is included.
(*) advanced cases

Papaioannou and Urban made a prospective study on 60 patients presenting with stage III and IV tumors with a mean tumor diameter of 8cm. They dissected the homolateral supraclavicular region, whether a node was palpable or not. In 15 of the 60 patients (25%), a node was clinically present and positive in 12/15. Pathology was positive in 16 (35%) of the 45 clinically negative patients, giving a total of 50% positive nodes. There were proportionally more positive SCN for the centrally located tumors (15/21 or 71%) than in the other sites. In all these patients, extensive invasion of the axillary nodes was reported

As is well known for the axillary region, this demonstrates that also for SCN a discrepancy exists between clinical examination and the pathology report. The same range of incidence is quoted in the further discussed series where the influence of adjuvant radiotherapy is examined.

Kiricuta et al. reported on 795 'operable' patients and stated that 2.6% had a SCN. Of the 20 patients presenting a SCN, 7 had Tl-T2-tumors. However, the total number of the patients in each T-category was not stated. Updating their series, they reported later on 55 patients with a SCN recurrence (Willner et al.). Of these, 53% concerned a median tumor and 37% in an external quadrant. In 25 patients the tumor-location was unknown. The total number of patients primarily treated was not reported. Of these 55 patients, 23 had initially received adjuvant radiation therapy 'using different fields' including the SC-region in only 14 patients. Recently, Perez and al. reported an incidence of 13% in 281 advanced cases of non-inflammatory breast cancer. Data on the correlation between tumor location and incidence of SCN were not found in the available literature.

We conclude that the frequency of SCN at presentation is between 1 and 10%. For larger tumors, as shown by Papaioannou et al., it increases up to 50% when the pathology of the nodes is included. A somewhat higher incidence of SCN is reported in medially situated tumors. Any correlation with estrogen receptor-status is not reported in the literature.

An important fact i,s however, as seen in table 8.80, that the incidence of SCN has gradually decreased over the past 100 years. We all have observed that the mean diameter of the tumors at presentation has dramatically decreased, resulting in lower stages and a lesser likelihood for SCN.

Incidence of SCN in the subsequent evolution

Metastases to the SCN can occur as a first event in the follow-up, or subsequently during further evolution with or following other metastases or only be found at autopsy. This is not always clear in the reported series. Notwithstanding the fact that the length of the follow-up is not always reported, its incidence seems to vary between 12 and 22% (table 8.81)

Table 8.81 - Breast Cancer
Incidence of SCN in follow-up
Literature Review by the author

Author	N	N-SCM	percent
Dahl-Iversen	109	29	21%
Luff	227	28	12
Haagensen	640	89	14
Röden	139	29	21
Ducuing	257	57	22
Andreasen	63	14	22
Boyd	679	85	12.5
Jackson	1461	174	12
Bunting	596	64	10.7
Bedwinek	936	42	4.5(°)
Crowe (stage II)	318	24	7.5

(°) only patients without other metastases

Jackson was the first to correlate the incidence of SCN with the pathology of the axillary nodes at first treatment. He observed an increase from 7% with a negative axilla to 20% when they were positive.

Bunting et al. treated 596 patients with operable breast cancer, of which 75% were stages I-II, with postoperative radiotherapy on the chest wall and SC-region. They observed within 5 years a SC recurrence in 10.7% of all patients, proportionally more with grade III tumours (37% of the nodal recurrences) than in grade I, where only 14% of the nodal recurrences were in the SC-region. This is the only report relating grading of the tumors with SC recurrence. Kaae et al. observed 15% SC-recurrence in patients with positive nodes but only 1% when the nodes were negative. Fentiman et al. report that 75% of their 35 patients with a SCN previously had a positive axilla.

Some authors have reported on the mean time interval between first treatment and the occurrence of a loco-regional recurrence (table 8.82). A SCN appears certainly later than an axillary recurrence, what could be explained by the lymph flow dynamics (Willner et al.). They can occur more than 7 years after primary treatment.

Table 8.82 - Breast Cancer
Mean time interval for a locoregional recurrence
Data of Fisher et al.

Author	Breast	Axilla	SupraClav
Fowble	28.5mos	15mos	34mos
Pierquin	24	14	32
Spitalier	--	24	---
Clark	--	--	36

According to Hirn-Stadler et al., 75% of the SCR appear within 3 years after surgery, with a mean interval of 26 months. Schultz et al. mention 90% within 3 years.

Kiricuta reports that 42% of the SCN occurred within the first 2 years, but 80% within 5 years and in 8 patients after 7 years. Evaluation of the patients characteristics showed a high proportion of positive axillary nodes status (65%) at primary diagnosis. The recurrence pattern in 318 stage II patients was examined by Crowe and al. after mastectomy and chemotherapy, with or without hormonal therapy (tamoxifen). A supraclavicular node was observed as first recurrence in 19 patients and in 5 more subsequently, giving an rate of 7.5% in all patients, but 30% of all locoregional recurrences. Finally, we can quote that Harnett found a SCN in 16% of the mammary cancer patients who came to autopsy. More details on these patients were not reported.
From the few data in the literature, the fact emerges that the pathology of the axillary node is a strong indicator of risk for the occurrence of a subsequent supraclavicular node metastasis.

Cervical Nodes

Cervical lymph nodes can occur as the first manifestation of breast cancer, even in 0.3% before the diagnosis of the primary was made. Herrman reported on five patients with upper cervical lymph node metastases, of which one heterolateral. In none of them supraclavicular nodes were present.
Nodes in the parotid and/or pre-auricular region are rather rare. They all can occur without the presence of supraclavicular nodes, but they are frequently part of a widespread disease. Large cervical nodes can cause a Claude-Bernard-Horner syndrome.
Data on the incidence of non-regional lymph node metastases were reported in an autopsy study by Cifuentes et al. The high rate of abdominal and pelvic nodes is remarkable (table 8.83).

Table 8.83 - Breast Cancer
Incidence of Non-Regional Lymph Node Metastases
(N=707) Data of Cifuentes et al.1979

Cervical	63%
Thoracic	45
Abdominal	59
Pelvic	79
Other Sites	62

Sentinel Nodes

A sentinel node receives the first lymph drainage from a primary and will most probably be the first site of lymph node metastases. This node can be identified by different methods as with vital dye or radionuclides.

In an effort to spare as much as possible to patients the invasive axillary dissection, the method of detection of a sentinel node has gained some favor, as it can in case of negativity dispense the patient from further surgery (table 8.84). Experience proves that the status of SN accurately predicts status of axillary nodes and has also a good negative-predictive value.

Table 8.84 - Breast Cancer
Basics on Sentinel Node Biopsy

Advantages
1. Fast evaluation of regional stage
2. Less Overall Morbidity with elimination of axillary dissection in 75%.
3. Radioactivity and/or dye guides the surgeon, resulting in optimal site of incision
4. Radioactivity evaluates completeness of excision
5. Detects non-axillary nodes

Disavantages
1. The technique is challenging
2. Drainage can occur in other locations
3. False negative, although rare, possible
4. No Long-term data
5. Previous surgery (tumorectomy) can distort flow

Anatomo-clinical evidence should point to the fact that in breast cancer not only the axillary nodes can be a sentinel node. Some recent series have observed that this occurred in between 5 and 25%, but only Jansen et al. have recently provided adequate data. Extra-axillary nodes as sentinel nodes were much more frequently associated with tumors located at the inner half, as could be presumed, but their demonstrative data were confirming, although more data should be wellcome (table 8.85). The tumors at the inner half have clearly more extra-axillary sentinel lymph nodes.

Table 8.85 - Breast Cancer
Site of Sentinel Nodes (N=113, with 100 positive)
Modified from Jansen et al.

	N	Axilla	Ax+Other	Non-Ax only
	113	N=79	N=18	N=3
T1-N0 (')	55	69%(")	16.3%	5.4%
T2-N0	52	75	11.5	--
T3N0	6	33	(50)	--
Upper Outer	48	81.2(°)	12.5	--
Lower Outer	20	70.0	5.1	--
Upper Inner	22	54.0	18.2	4.5%
Lower Inner	10	40.0	30.0	20.0
Central	13	77.0	15.4	--

(') UICC stage; (") % of the T-group;
(°) % of the site group

Distant Metastases

Breast cancer metastasizes in almost every organ. Many organs are, however, more involved than others. The involvement of the different organs differs according to the primary. .

Autopsy studies have been reported. Data from patients treated in recent decades are, however, almost inexistant. Is it due to an overall decline of the autopsy-rate be the reason, or to a decrease in interest specifically for breast cancer autopsies? Data concerning the influence of the actual modern chemotherapy on metastasis distribution are not at hand.

We have collected some interesting data from the literature, but they should currently be actualized.

Table 8.86 - Breast Cancer
Comparison of Metastases In-vivo and at Autopsy
N=169 Data of Hagemeister et al.

Site	Ante-Mortem	Autopsy	Differ.
Soft-tissue	50%	36%	9%
Respiratory	47	75	28
Osseous	57	67	10
Hepato-biliary	42	71	30
CNS	26	30	14
GIT	8	35	27
Endocrine	5	46	40
GenitoUrinary	1	22	21
Cardiac	12	22	20
Ophthalmic	<1	<1	--

Based on the autopsy data on 169 patients who have died of BC, Hagemeister et al. compared the knowledge of metastases during clinical evolution with the data remarked at autopsy (table 8.86). As the study was reported in 1980, one should keep in mind that clinical data were not completed in that period by the imaging method we presently have. Nevertheless, the difference is striking for thoracal, hepatobiliary and GIT-locations.

Table 8.87 - Breast Cancer
Site of first Recurrence

Site	Bunting(')	Kamby(")
Distant Skin	11%	--
Pleura	22	10%
Mediastinum	8	5
Lung	20	18
Liver	30	15
Other abdomen	6	--
Brain	5	3
Bone		32%
Skull	6	
Spine	42	
Ribs-Scapula	16	
Arm	2	
Leg	12	

(') 348 patients (") 415 patients

A number of authors have reported on the site of first recurrence (table 8.87).

From a large series of 415 patients, Kamby et al. remarked that locoregional recurrences were proportionally more frequent during the first three years, while distant metastases were more frequent in the later evolution (fig.8.16).

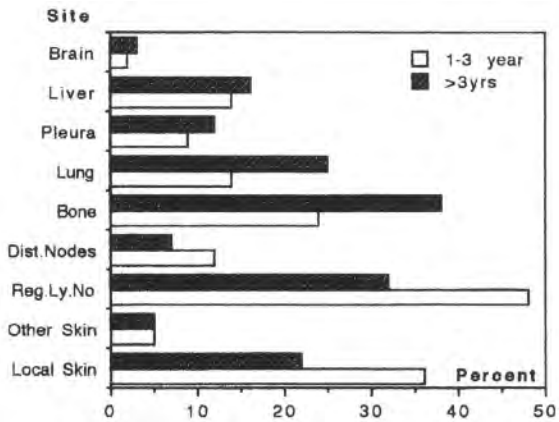

Fig.8.16 - Site of first recurrence according to the length of disease-free interval in 188 patients within the first 3 years or in 213 patients after 3years. (Redrawn from data of Kamby et al.)

Table 8.88 - Breast Cancer
Distant Metastases at Autopsy

Site	Cho N=144 (°)	Lee	Parham N=85	Kamby (§)	Cifuentes N=707
SupraDiaphragmatic					
Lung	60%	71%	21%	19%	67%
Pleura	36	50	27	12	50
Brain	26	22	5	4	31(CNS)
Meninges	16	--	3	--	--
Diaphragm	15	--	--	--	--
Heart	--	--	10	--	11
Infra-Diaphragmatic					
Liver	53	62	22	9	62
Adrenal	36	41	5	--	41
Spleen	18	--	1	--	15
Stomach	18	--	4(*)	--	16(*)
Abdomen	18(')	67(")	12(")	--	--
Pancreas	16	--	--	--	13
Ovary	15	21	1	--	21
Small intestine	14	--	--	--	--
Kidney	13	--	2	--	14
Other					
Bone	54	71	20	--	71
Varia	6	--	--	8	--

(') mesenterium, omentum and peritoneum
(°) mean of 7 series ante 1983, only 10 leading sites, including breast, skin
(§) average of 37 clinical studies, 1990
(") abdominal and thoracal nodes
(*) GIT

Several series have reported on the metastatic distribution observed at autopsy (table 8.88). The most complete and detailed data, as data on side and of the different anatomical structures, have been reported by Cifuentes et al. in a report dating backto 1979. While

there is relatively good consensus on the incidence for the 'major sites', data on the other sites are clearly indufficient.

Influence of Pathology Factors

Histology

Several authors tried unsuccesfully to find a relationship between histological subtype of ductal carcinoma and the location of metastases.
In the last decades, after Foote et al. had given the first description of the lobular carcinoma in situ, the invasive (ILC) counterpart was recognized with a reported incidence of 1 to 20% of all breast cancers.
Harris et al. demonstrated the propensity of ILC to metastasize more frequently to some unusual sites such as the peritoneum, the retroperitoneum, hollow viscera and the leptomeninges. Comparing 830 patients with ductal cancer with 135 invasive lobular carcinoma, they found a statistical difference between some metastatic sites according to histology.

Parenchymal lung metastases were more frequent in ductal cancer, whereas bone, meningeal and peritoneal-retroperitoneal metastases were much more frequent in lobular cancers. As discussed further, this histology type frequently causes a linitis-type of infiltration and invasion in the abdominal cavity.
The data of Dixon et al. were only relevant for peritoneal and liver metastases, with more in the lobular type group. More detailed data were reported by Lamovec et al. in an autopsy study in respect of 220 patients (table 8.89).

Table 8.89 - Breast Cancer
Difference in Metastases according to histology
(only significant differences) (N=220)
Data of Lamovec et al.

Site	Lobular N=25		Ductal N=195	P
Lung	40%	<	70.3%	<0.006
Myocardium	28.0	>	1.0	<10exp-6
Meninges	12.0	>	1.0	<0.006
Stomach	20.0	>	3.6	<0.004
Intestine	40.0	>	2.0	<10exp-6
Ureter	32.0	>	3.6	<10exp-5
Urinary Bladder	12.9	>	1.5	<0.002
Uterus	52.2	>	0	<10exp-6
Ovary	52.2	>	11.3	<10exp-6
Peritoneum	60.0	>	15.4	<10exp-6
Retroperitoneum	60.0	>	6.7	<10exp-6

Based on a much larger number of patients (1,238), Jain et al. observed fewer pulmonary and pleural metastases and brain metastases in lobular cancer patients, while they had significantly more peritoneal, bone and bone marrow metastases, only partially confirming the data of Lamovec. However, only a limited number of sites were studied.
Comparing 359 patients with lobular cancer with 2,246 ductal cancers, Borst et al. observed a similar trend (table 8.90).
On the other hand, DuToit et al. were not able to find a significant difference when comparing 171 lobular with 342 ductal cancer patients.

Comparing 100 patients with a relapse in the first 8 years after first treatment with 100 patients relapsing after 8 years, Basso-Ricci et al. observed that in the first group there were only 9% lobular cancers, but 25% in the second group. Unfortunately, they did not correlate the type of recurrence with the histology

Table 8. 90 - Breast Cancer
Difference in Metastases according to histology
(only significant differences) (N=2605)
Data of Borst et al.

Site	Lobular		Ductal	P
GIT	4.5%	>	0.2%	<0.001
Gynecologic	4.5	>	0.8	<0.001
Peritoneum	3.1	>	0.6	<0.001
Adrenal	0.6	>	0	0.019
Bone Marrow	21.2	>	14.4	0.001
Lung-Pleura	2.5	<	10.2	<0.001

A drawback of the forementioned studies is the relatively low number of lobular cancer patients included for comparison with the larger number of ductal cancers. A study comparing an equal number (2x188) of matched patients, was reported by Fondrinier et al. Essentially the same conclusions were obtained (table 8.91) as hepatic, lung and brain metastases were significantly more frequent in ductal cancers, while metastases to the GIT, gynecologic organs and peritoneum were more frequent in lobular cancer.

Table 8. 91 - Breast Cancer
Difference in Metastases according to histology
(only significant differences)
Data of Fondrinier et al.

	Overall		First Recurrence	
	Duct	Lob.	Duct.	Lob.
Site	N=188	N=188	N=188	N=188
Lung	7.9%	3.2%	NS	
Liver	11	3.2	22%	3.0%
GIT	0	6.9	0	8.0
Peritoneum	0	7.9	0	11.7
Gynecol.	0	6.4	0	10
Nerv. System	4.8	1.0	NS	

The metastatic distribution as obtained by imaging methods in 57 women with lobular breast cancer was recently reported by Winston et al. However, they did not compare the data with ductal cancer patients, but observed a relatively high number of GIT involvement.

Estrogen Receptor

There is a large literature on various aspects of the effect of the estrogen- and progesterone-receptor on the biology of breast cancer. We will only briefly report

on the few available data, as large (autopsy-) statistical data are not available.
Based on a study of 394 evaluable patients, Kamby et al. concluded that patients with ER+ tumors had recurrences more often in the bone, and ER- recurred more often in the liver.
Univariate analysis on 258 patients allowed to conclude to a statistically different metastatic pattern according on the ER status. Patients with ER+ tumors had bone metastases three times more frequently. Visceral metastases were 50% more frequent in receptor-positive tumors. A multivariate analysis showed that the receptor was the only influencing factor (Koenders et al.).
Based on 100 patients, Maki et al. conclude to two groups of patients, depending on receptor status. The patients with ER+/PR+ tend to develop more osseous but no brain metastases, while ER-/PR- have the opposite pattern.

Influence of Stage of Disease at Diagnosis

Kamby et al. have examined this factor. They observed a shorter recurrence-free interval in stage II than for stage I patients, with an understandably higher number of metastatic sites in stage II patients.
Although staging work-up with the various imaging methods, at least for asymptomatic and low-stage tumor patients is presently somewhat controversial, the data obtained are interesting and confirm the low rate of metastasis in these patients.

Reporting on 1,017 patients without complaints that might indicate some metastases, Ciatto et al. observed that a Chest X-ray was positive in 0.29% and a bone study in 0.59%. Depending on loco-regional stage of disease, they found metastases in 0.36% at stage I, 0.20 at stage II, in 0.26 for grouped stages I-I, but in 2.77% for stage III patients.

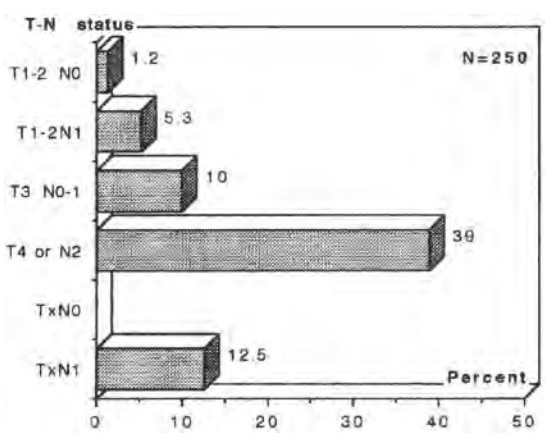

Fig.8.17 - Detected distant metastases in 250 patients according to T or N stage (Drawn from data of Samant et al.)

Reviewing 250 patients at presentation, Samant et al. have clearly shown the influence of stage at presentation on the incidence of any distant metastasis (fig.8.17). Overall, only 10 % of the patients had a metastasis, but when tumor and/or N-stage is considered, the differences are striking but not unexpected. On the other hand, most patients (84%) had overt clinical symptoms, so that imaging could only add the 16% of the asymptomatic patients, or only 4 of the 25 confirmed patients, making only 1.6% of the whole group.

Influence of Adjuvant Chemotherapy

The purpose of adjuvant chemotherapy after first surgery and/or radiotherapy is to prevent or, at least, to postpone recurrences and/or distant metastases as much as possible. Although many thousands of woman have undergone this treatment, data on the metastatic pattern have hardly been reported. As the 'usual' pattern is not known adequately, differences will be difficult to observe or objectivize.

Kamby et al. have studied the patients of a large Danish trial and could observe a some lower overall metastatic rate, but more liver metastases. Particular drug combinations resulted in an increase of lung metastases, while others had fewer lymph node and pleural recurrences compared with the control group. It is not clear wether it merely indicate a retarding effect or an overall lower rate, as they did not note the time-sequence of the metastases. We are not aware of autopsy data.
In a later report, the same authors mention a relative reduction of 37% for local recurrences and of 25% for distant metastases. The time-lapse was however not given, as the rate could only be post-poned in its evolution.

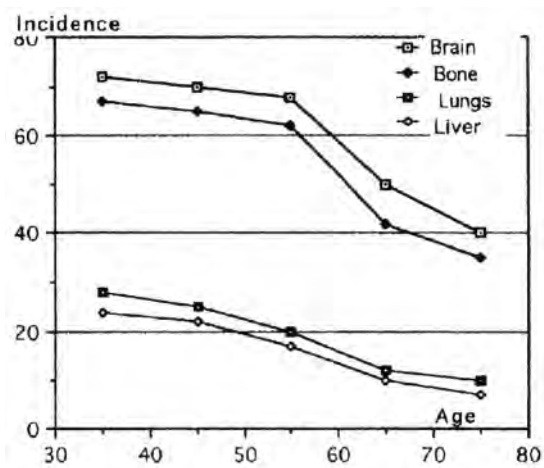

Fig.8.18 - Breast cancer : Incidence of metastases according to age of the patients. (Drawn from data of Basserman et al.)

Influence of Age

Although a number of authors remark that there are some differences according to age groups, data are almost never reported. From the data of Basserman et al., we were able to draw a graph confirming the age factor, showing a progressive decrease in the incidence of the different most frequent metastatic sites (fig. 8.18). Similar data reported later by delaMonte et al., but extended to more sites, confirmed the de-clining trend the incidence of metastases acording to age.

Thoracal - Mediastinal Lymph Node Metastases

In the autopsy series of Cifuentes et al., thoracic nodal metastases were observed in 45% of the 707 patients. The involvement of the intrathoracal lymph nodes is well known, but a systematic study has rarely been performed. Thomas et al. studied 26 patients at autopsy and could observe some features (table 8.92 and fig. 8.19).

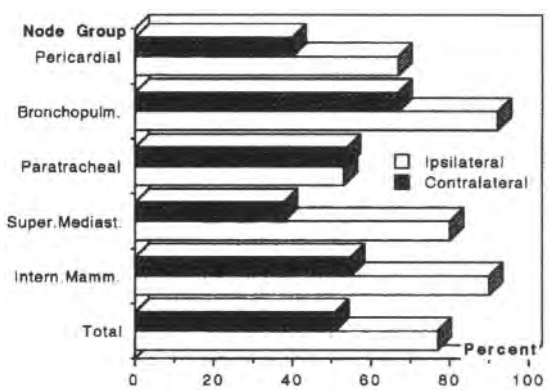

Fig.8.19 - Comparative involvement of the ipsi- and contralateral intrathoracal lymph node groups in 26 autopsied patients (Drawn from data of Thomas et al.)

Their findings confirm that the clinical patterns of pleural and mediastinal involvement are caused by lymphogenous dissemination. Breast cancer spreads along the internal mammalian nodes to the other intrathoracal sites as the mediastinum, the pleura and the lungs. When the lung is involved, the number of involved groups will be much higher than when the lungs have nor been invaded.

It must be said that the reverse is also true: the higher the number of mediastinal nodes involved, the higher the observed frequency of pulmonary involvement. This allows to conclude that lung invasion occurs most probably from the tracheobronchial node, as lymphangitic involvement is observed in 83%, the other 17% having tumoral infiltration only. The same applies for the pleural with 71% lymphangitic and 26% only infiltration. The data on pulmonary and pleural were not separated however, according to ipsi- or contralaterality.

Table 8. 92- Breast Cancer
Intrathoracal Spread (N=26 autopsies)
Data of Thomas et al.

Status of Lung	N(')	Number Invaded 1-3LyGr	>3LyGr
No Metast.Disease	12	67%	33%
With IntraLymph.Dis.	35	26%	74%

Negative Lung 7/12 -58% Ipsilat.TracheoPulm.Node
Positive Lung 34/35 - 97%
(') number of lungs

One patient (F47) has been reported as presenting with cough and progressive dyspnea. A chest X-ray showed mediastinal and bilateral hilar adenopathies. The diagnosis of sarcoidosis was suggested, but one year later the patient presented with a T3 breast cancer and axillary nodes (Urschel et al.).

Data on First Event (after first treatment)

The sequential chronology of metastatic events has virtually not been studied. As one of the exceptions, data on the first event, without mention of time interval, was reported by Lê et al. in the follow-up of 1,195 patients with tumors up to 7 cm in diameter and surgically treated with or without radiotherapy (table 8.93).

Table 8.93 - Breast Cancer
Site of First Metastatic Event and Incidence (N=1,195)
Data of Lê et al.

Site of Distant Metastasis	Frequency
Unique	
Bone	16.9%
Lung	10.9
Liver	4.2
Distant Lymph node	2.3
Brain	0.8
Other sites	0.2
Multiple sites	5.8
Any site	43.3
Contralateral breast	6.3

Surprisingly, almost no data are available concerning time-lapse studies on the incidence of distant metastases after first treatment. Although they did not report on specific sites, Koscielny et al. have published a graph on 4,000 patients, with a folllow-up of up to 20 years (fig.8.20). While metastases are frequent in the first two years, they found that nearly 90% of the subsequent metastases do not occur in the first year. When only the grade I cancers are examined, a clearly wave-like graph is obtained. The authors explained this in terms of a progression of grade I tumors to grade II, the tumors becoming more aggressive and metastasizing later.

Pulmonary Metastases

The literature on pulmonary parenchymal metastases

from breast cancer is rather limited compared to the amount of reports on pleural metastases. This is probably due to the limited treatment possibilities.
Schlappack et al. were able to find only 50 (7%) with exclusively lung metastases in a series of 672 breast cancer patients.

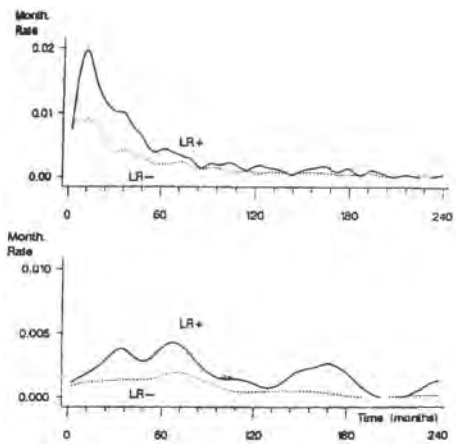

Fig.8.20 - Monthly rate of distant metastases emerging after first treatment. Upper curves relate to all patients, while the lower relate only grade I tumors (LR- means no locoregional recurrence, LR+ with locoregional recurrence (from Koscielny et al., with permission)

Gawne-Cain et al. reviewed the chest X-rays of 92 patients who developed any type of thoracopulmonary problem, and found pulmonary metastases in 32% of the patients (table 8.94). The data at autopsy are much higher, with 75% pleural and 80% lymphangitis carcinomatosa (Connolly et al). The high incidence of lymphangitis corroborates the above-mentioned data of Thomas et al.

Table 8. 94 - Breast Cancer
ThoracoPulmonary Metastases at Chest X-rays
Data of Gawne-Cain et al.

	N=88	N=41 single(')
Normal image	23%	
Pulmonary nodules	66%	32%
	1-5 : 41%	
	>5 : 59%	
Pleural Effusion	41%	10%
unilateral 55%		
bilateral 45%		
Mediastinal adenopathy	25%	1%
Lymphangitis carcinomatosa	18%	3%
Pleural nodules	11%	---
Bony metastases	19%	

(') only at one site

Reviewing the records of 1,486 patients, Virkkunen et al. observed pulmonary metastases at staging in 115 or 7.7%. About half of the patients were asymptomatic. The number of metastases within the parenchyme did not differ between both groups. The size of the metastases varied from 1 to 40 mm, but data on the number counted were not reported.

The appearance usually regarded as a metastasis. The development of surgery, however, has led to the observation, that a number are benign nodules and quite another are a new bronchogenic carcinoma. This should be appreciated as the problem of the coin lesion, as discussed in chapter 1. Some data are on table 8.95.

Table 8. 95 - Breast Cancer
Solitary Pulmonary Nodules
Literature data

	Meta	Benign	New Primary
Cahan 1975	23	6	43
Saegesser '79	4	1	2
Casey 1984	18	2	22
Total	45 (37.2%)	9	67(55.5%)

We are not aware of more recent data, but the progressive increase in bronchogenic carcinoma in women in recent decades will probably result in the same trend.

Spontaneous pneumothorax has been reported in metastatic breast cancer, but at a much lower rate than for sarcomas. In two cases reported, it occurred after intensive chemotherapy (Brufman et al.; Bini et al.).

Sudden dyspnea and chest pain is, as discussed in Chapter 1, must be related to other frequent complications, as the rarely occurring acute pulmonary tumor infarct. Frequently reported in other cancers, it is relatively rare in breast cancer (Abbondanzo et al.). CT and aspiration cytology were able to confirm the diagnosis in one patient (Chan et al).

Metastasis to the Pleura - Pleural Effusion

This is the most frequent thoracic complication of breast cancer. It is due, as discussed above, to contiguous spread from the thoracic wall or internal mammary nodes, most ipsilaterally but subsequently contra-laterally. It should not be considered a distant metastasis.
It is present at autopsy in more than 80% of the patients and will be found progressively during follow-up in most of the patients. The time-interval can extend up to 10, even 20 years (El-Mahdi et al.). There is no clear correlation with positivity of the axillary nodes, as the malignant cells will usually proceed mostly along the internal mammary nodes.

According to the different series, the pleural effusion will be ipsilateral in about 60-70% of the cases contralateral in 25%, with bilaterality in the other (Raju et al.; Fentiman et al.).

Although no longer routinely applied, thoracoscopy is able to evaluate the involvement of both pleural blades separately (table 8.96). The data point towards a more frequent pulmonary 'origin', as the visceral pleura is

involved in 59% and the parietal in only 15%. This raises the possibility that pleural effusion is more frequent secondary to a pulmonary (lymphangitic) involvementthan of an invasion of the chest wall.
Reviewing six patients with pleural effusion investigated by means of the thoracoscope, Levine et al. observed seeding of the pleural space with metastatic deposits that could be biopsied. They did not report separately on pleural blades each.

Table 8.96 - Breast Cancer
Pleural Metastases evaluated at Thoracoscopy (N=46)
Data of Fentiman et al.

	Total	Ipsilat.	Contralat.	Bilateral
No Tumor seen	12	7	3	2
Visceral tumor	27	15	6	6
Parietal tumor	7	4	2	1

Cytology is of course the mainstay for the diagnostic confirmation, but a negative cytology does not constitute a final diagnosis. CT is presently the best imaging modality for delineating the situation of the mediastinum and the pleura, simultaneously with the lung parenchyme.

Pulmonary Lymphangitis Carcinomatosa

This metastatic situation most probably originates through infiltration from metastatic mediastinal lymph nodes into the pulmonary parenchyme (see above).
This is a frequent complication and relatively easy to diagnose, if radiology shows the typical pattern, but in some cases the involvement is only lobar or multisegmental. The clinical picture of progredient dyspnea, dry cough, sometimes complicated by tachypnea, tachycardia and cyanosis is rather typical.
Presently, the diagnosis can be confirmed by transbronchial fine needle aspiration cytology or biopsy. Radiology can be supplemented by nuclide scintigraphy that can show aspecific vascular defects and by adequate CT-techniques.

Table 8.97 - Breast Cancer
Endobroncheal Metastases - Cases Reported

Author	Patient	Bronchus	Symptom	Interval
Garces 1974	F35 Ri	LLL	Cough	16 mo
Krutchik 1978	F53 Ri	LUL	Cough	20 mo
Krutchik 1978	F36 Ri	RUL	Cough	8 mo
Krutchik 1978	F54 Le	RUL	Hoarseness	84 mo
Krutchik 1978	F72 Le	RLL	Cough	8 mo
Krutchik 1978	F33 Ri	RLL	Cough	21 mo
Krutchik 1978	F60 Le	LUL	Hoarseness	68 mo
Daskalakis '81	F31 Le	LLL	Dyspnea	2 yrs
Ettensohn '85	F78 Le	LLL	Cough	8 yrs
Ettensohn '85	F26 Le	RUL	None	1 mo
Ettensohn '85	F68 ??	RUL	Cough	13 yrs
Ettensohn '85	F76 Le	RML	Cough	10 yrs

The pattern of recurrence within the thorax was examined by Kamby et al. They observed that multiple round infiltrates were the most frequent presentation, as were ipsilateral pleural effusions, but pleural tumors were never without effusion (table 8.98). The occurrence of intrathoracal metastases was many times associated with other sites (table 8.99).

Table 8.98 - Breast Cancer
Intrathoracic Recurrences (N=401)
Data of Kamby et al.

Site	Lung N=77	Pleura N=42	Mediast N=22	All N=401
Local skin	14%	21%	14%	28%
Distant skin	6	14	5	5
Reg..nodes	27	31	36	39
Other nodes	18	19	50	10
Contralat.Breast	6	5	9	4
Bone	34	38	41	31
Lung	--	38	59	19
Pleura	21	--	23	10
Mediastinum	17	12	--	5
Liver	18	17	32	15
Brain	1	0	9	2

Table 8. 99 - Breast Cancer
Intrathoracic Recurrences
Data of Kamby et al.

Pulmonary (N=77)		Pleural (N=42)	
Round infiltrates	90%	Effusion	87%
Lymphangitis	5	Tumor	0
both	5	both	13
Solitary lesions	27	Unimateral	79
Multiple	73	Bilateral	21
Unilateral	29	Ipsilateral	83
Bilateral	71	Contralateral	17

Endobronchial Metastases

In a consecutive series of 1,628 patients with breast cancer, Krutchik et al. found six cases with endobronchial metastases, all with grossly visible lesions and confirmed at histology. In three of them it was the first sign of a recurrent breast tumor. In the other, the interval was 8 to 84 months with a mean of 21 months. Some reported cases are in table 8.97.

Table 8. 100 - Breast Cancer
Endobroncheal Metastases
Indications for Bronchoscopy Data of Tenholder et al.

	N	Lesion	Biopsy+
Complaint			
Hemoptysis	1	1	1
Recent cough-wheezing	1	--	--
Chest X-ray finding			
Localized infiltrate	1	--	--
Lobar collapse	4	3	3
Diff.interstit.disease	5	4	3
Peripheral nodule	3	--	--
Hilar adenopathy	1	1	--
All patients	16	9	7

Some additional series have been reported. Albertini et al. published on 10 patients aged between 47 and 58years. In a short report on 16 patients, Tenholder et

al. provided interesting data, particularly on the symptomatology leading to the bronchoscopy (table 8.98). Abnormal findings on chest X-rays were the main cause for the investigation, indicating that many patients are asymptomatic.

Cardiac Metastases

If about 10% if the patients have at autopsy cardiac involvement, myocard metastases are rare in BC and almost not reported. On the contrary, pericardial effusion, sometimes complicated with tamponade has been reported, but also in a much lower number than for other primaries, such as bronchial cancers.
The pathway, as now generally accepted (Chapter 1), is penetration of malignant cells from mediastinal lymph nodes to the posterior surface of the pericard.

Hirsch 1966	F34	Ri.Carc	Acute dyspnea	5yrs
Almagro '82	F47	Le.Duct	Tamponade	simult
DeSchepper '00	F76	Le.Carc.	Dyspnea	28 yrs

From a large series of breast cancer patients (N not given), 90 patients were found at echocardiogarphy to have pericardial fluid (Buck et al.). In 70, the presence was suspected at chest X-rays, in 32 of whom it was the sole problem, with no confirmed pericardial or any other metastases. In only half of the 38 other patients, the malignancy was confirmed at cytology or histology.
From a series of 2,700 patients with breast cancer, 19 patients presented with signs of pericardial effusion and thos wasconfirmed. Almost all had already been treated for other metastatic sites (Swanepoel et al.).
This corroborates the conclusions put forward by Buck et al. after having reviewed 90 patients with a positive echocardiogram. A small effusion is common in any patient with evolutive breast cancer and no effusion was observed when the patient was free of metastatic disease. When, however, metastatic disease is present, cytology-positive effusion in the pericard is seen in 50%.

An unusual case was reported by Fortt et al. A woman presented with increasing dyspnea 3 years after mastectomy. Except for a right basal pleural effusion and possibly a pericardial effusion, nothing unusual was noted. The report must have predated the echocardiography era, as at autopsy a thickened and firm tricuspid valve ring was noted, with a large tumor involving the myocardium and extending to the endocardial surface and towards the pericard.

There is a much more concern about cardiac problems secondary to radiotherapy and to the various modern drugs utilized in chemotherapy than for those caused by metastatic spread.

Metastases to the Skin

Breast cancer is regularly cited as being the main cause of skin metastases. However, almost all skin metastases over the thorax are lymphogenic and in fact not to be considered distant metastases. They must be differentiated from thoracic wall recurrences (see also fig.7.2). Progression over the abdominal wall and the back is also regularly seen.

Several clinical forms of skin metastases have be observed. They have been well described by Freid.
1. Single or multiple cutaneous nodules with some reddening of the skin. There is progressive invasion of the skin with retraction, ulceration and crusting. Later some adjacent nodules will coalesce;
2. Crops of nodules with apparently intervening tissue may appear over a wide area including the thoracic or abdominal wall;
3. A picture of diffuse nodular spread combined with intense fibrosis, well-known as 'cancer en cuirasse'. The chest wall will become constricted and indurated with trawny, irregular skin, which may ulcerate later;
4. A large mass can grow exuberantly out-wards, with forthcoming ulceration.

Metastases in the skin of the H&N region are relatively rare. Most arise on the scalp, but can also present on the face and in the neck. They can occur as isolated, unique metastases, though they are often part of a widespread disease.

Head and Neck Metastases

The large number of other pathologies and diagnoses which are, in fact, much more frequent in that anatomical region, will sometimes pose the difficult problem of differential diagnosis.
Indeed, neurologists, ophthalmologists, stomatologists and otolaryngologists will be consulted and confronted by these patients. If they are not familiar with such oncological unusual problems, the diagnosis may be delayed or even missed.

The incidence rate of H&N metastases from breast cancer is in fact unknown. Data can hardly be found in the literature and not easy to register. Many metastases, however, will remain undetected, as they can be 'obscured' within an overall clinical metastatic picture with more severe symptoms and with a large number of other more prominent metastases. Autopsy data are of course more complete, but they depend on the diligence and the meticulousness of the pathologist.

Metastases in the H&N region are hematogenous, along the arterial route. The classical venous route of Batson along the prevertebral venous plexus could be another pathway.
They can occur in the tonsil, the tongue and the larynx. Even more rare are pharyngeal and gingival metastases. They must be differentiated from new primary tumors occurring in that region. Histological study will reveal the epidermoid nature of the latter,

whereas metastases from breast cancer are of the adenocarcinoma type.
The clinical symptomatology of all these metastastic localizations is local pain, complicated with specific local complaints such as nasal problems, dysphagia or the feeling of a tumor within the oral or pharyngeal cavity.
Clinically, it is always a submucosal tumoral infiltration, relatively difficult to biopsy, due to the overlying normal mucosa. They can, however, nicely be shown on CT-studies.

Nelson reported the first case of metastases within the ethmoid sinus from a breast cancer. Reviewing the literature, he collected 97 cases from other primaries. There are also reports on metastases within the nasal cavity. One rare case of metastasis in the frontal sinus was reported by Myers.
Surgery confirmed metastatic foci in both ethmoidal sinuses and finally at autopsy at the skull base and meninges surrounding the cavernou!s sinus (Austin et al.).

Metastases to the tongue are usually located in the base of the tongue. Metastases to the pharyngeal wall have also been reported, one by Nguyen et al. and one by Biller et al. These metastases were located in the cricopharyngeal muscle (table 8.101).

Table 8. 101 - Breast Cancer
Metastases to the Oral Cavity
Cases Reported

Author	Patient	Site of Metastasis	Interval
Kolson 1966	F69 Ri.	Tongue (base)	2 yrs
Perlmutter '74	F44 Le	RiMax.gingiva	8 mo
Barton 1980	F33 Ri.	Le.Tonsil	11 mo
Nguyen 1983	F43 Le	Le.Sin.Piriformis	7 yrs(')
Sweet 1985	F35 Le	Gingiva Ri.	3 mo
Eckardt 1986	F38 Ri	Ri.max.gingiva	2 yrs
Perchick 1986	F57 Ri	Tongue left side	14 mo
Saab 1987	F58 Ri	Nasopharynx	8 yrs
Nelson 1990	F42 Ri	Ethmoid	16 mo
Needleman '92	F30 Le	Gingiva	18 mo
Wanamaker '93	F77 Le	Larynx (supragl.)	16 mo
Wanamaker '93	F44 Ri	Nasal septum	3 mo
McCarthy 1994	F45 Ri	Ri.Trig.Retromol.	I mo
Tueche 1999	F71 Ri	Le.Tonsil	24 yrs(!)
Nicol 2000	F54 Le(")	Floor of mouth	8 yrs

(') sole symptom of widespread metastases at autopsy
(") lobular carcinoma

Hoarseness is nearly always caused by a mediastinal involvement compressing the recurrent branch of the nervus vagus (Xth nerve). Metastases within the larynx are very rare indeed. However, they are frequently due to breast cancer. Ferlito et al. reviewed extensively the literature and found that almost 10% of these were due to a breast cancer primary.

Individual cases of ingival metastases have been described in the stomatological literature. Pearlmutter et al. reported the first case in 1974. The metastases must be differentiated from other new primaries but also from ulcerated metastases from within the bone, this condition being rather infrequent, however.

Table 8. 102 - Breast Cancer
Metastases to the Mandible or Maxilla
Cases reported

Author	Pat	Primary	Site of Meta	Interv
Adair 1946	F41	Ri.cancer	Mandible	3 yrs
Adair 1946	F63	Ri.cancer	Mandible	4 yrs
Adair 1946	F43	Le.Ductal	Mandible	5 yrs
Adair 1946	F51	Le.cancer	Mandible	2 yrs
Adair 1946	F50	Le.cancer	Mandible	3 yrs
Agerberg 1974	F46	Le.Ductal	Mand.Cond	2 yrs
Zachariades'82	F52	Ri.Carcinoma	Mandible	n.d.
Zachariades'82	F57	Le.Carcinoma	Mandible	15 yrs
Yagan 1984	F65	Ri.Ductal	Mandible	16 mo
ElDibany 1984	F42	Le.Lobul.	Maxilla	2 yrs
Shankar 1984	F44	Ri..Carcinoma	Mandible	11 yrs
Spott 1985	F51	??Carcinoma	Maxilla	2 yrs
Tenzer 1988	F68	Ri.Cystade	Maxilla	7 yrs
Zachariades1989	F41	Carcinoma	Mandible	8 yrs
Stavropoulos'93	F55	Ri.Lobul.	Mand.Cond.	7 yrs

Although common in patients with widespread bone metastases, mandibular or maxillary metastases can present as a single site of metastases, attracting much attention by the patient and sometimes perplexing the consulted doctor by its mimicking of the more common dental problems as periodontitis, pulp necrosis or even ameloblastoma. Several reports have indeed been committed to the difficult differential diagnosis (table 8.102). In some of the case reports, mention is made of other metastatic sites. Patients with metastases to the mandibular condyle are commonly mistaken for problems of the temporo-mandibular joints.

Metastases to the Salivary Glands.

Breast cancer has an unusual propensity to metastasize within the salivary glands, particularly the submandibular gland.

Table 8.103 - Breast Cancer
Metastases to the Salivary Glands
Cases Reported

		Breast	Gland	Interval
Submandibular Gland				
Solomon 1975	F60	Le	Ri	14 yrs
Moss 1983	F51	Ri.	Ri	11 yrs
Meyers 1984	F65	Ri	Ri	14 yrs
Rosti 1987	F68	Le	Le	4 yrs
Parotid gland				
Herrmann '49	F68	Ri	Ri	Reveal
Herrmann '49	F58	n.d.	Ri	Reveal
Wiesel 1982	F62	Le	Le	2 yrs
Wiesel 1982	F61	Le	Le	13 yrs
Wiesel 1982	F74	Le.	Le	8 yrs
Kollias 1997	F66	Ri	Le	4 yrs
Kollias 1997	F52	Ri	Ri	14 yrs
Kollias 1997	F57	Le	Ri	9 yrs

The largest series published, a German Study on tu-

mors of the salivary gland, found only 108 metastases from another primary in more than 10,000 tumors. Of these, only 5 were from a breast cancer, of which 3 actually were in the submandibular gland.
We have retrieved several cases from the literature (table 8.103). The long interval is to be noted, but also the fact that in 8 of the 12 reported cases, the metastases were on the same side as the primary.

Metastases to the Eye and the Orbit

Ophthalmological problems are not uncommon in the evolution of breast cancer. They firstly raise the problem of accurate diagnosis of the eventually metastatic cause and secondly, of the precise localisation of the metastases within the eye.

Font found that 50% of the orbital metastases are the first manifestation of a primary tumor, also of mammary carcinoma.
Any partial, sectorial, or total loss of the vision field in one or both eyes may be due to cerebral metastases in the occipital lobe (sulcus calcarinus). Metastases along the optical tract or at the pituitary region with involvement of the chiasma or optical nerves are another possibility. Meningeal seeding can also be the cause.
Skeletal metastases at the skull base including or only in the orbit, and metastases within the orbit, even in the ocular muscles can be uni- or bilateral. Bilateral orbital metastases have also been reported.

Diplopia is almost always caused by a paresis of the VIth nerve. Its involvement can be meningeal, at the skull base or in the orbit. Radiology and scintigraphy, but especially computer tomography or MRI are very sensitive methods for accurate location of the lesion.

When the cause is meningeal, many other neurological symptoms will accompany the clinical situation.
Some rare cases of metastases in the eyelid, even bilaterally have been reported. Up to 1973, only 11 cases had been reported. In 1988, Mansour reviewed the literature, found 88 cases and added another 49 from the files of the AFIP. Breast cancer accounted for up to 63% of all metastases in the eyelid, and 47% with both genders taken together (Mansour). Other rare locations of metastases are the epibulbar site, the iris and the corpus vitreum.

Choroidal metastases are the most frequent intra-orbital location of metastatic disease. They account for more than two-thirds of the ophthalmological metastases and for more than 90% of the intraocular localisation.

Some authors thought that metastases should be more frequent in the right eye due to more direct arrival of arterial blood via the right carotid artery. This was, however, not confirmed in most of the other series.

The choroidal metastases are, in fact, the smallest metastases that can be detected in vivo. Fluoroangiography is claimed to detect metastases of 1 to 2 mm^3 (Merrill et al.). Most reports discuss one aspect or one location of the opthalmic metastases.
The relative incidence in the various parts of the eye and/or orbit is difficult to evaluate. Hutchison et al. state that 65% of the ophthalmic metastases are situated in the choroid, 24% in the orbit and 10% 'elsewhere'.

The most frequent first symptom is partial or complete vision loss (80%), pain in about 14% and another 13% report photophobia or scotomas. The symptoms are bilateral in about 20% of the patients (Stephens et al.). Albert et al. made a prospective study in patients with breast cancer. They found choroidal metastases in 20% of the patients, half of them with no complaint at all.

Hennequin et al. have proposed a grading system for reporting the extent of the choroidal metastases: grade I means less than a quarter, grade II more than one quarter and grade III includes loosening of the retina. This classification was later modified by Panizzoni et al. considering halves of the retina.

The sector of the choroid most involved is the temporal one where 75% of the metastases are located, according to Tatcher et al., in 40 a study of patients.
Choroidal metastases can be the first symptom (Gross et al.) of an unknown mammary tumor. It can, however, also occur many years, even more than 20 after the diagnosis of the primary. (Field; Dejean et al.).
Exopthalmia is rarely caused by metastatic processes in breast cancer, but almost always asymmetrical. The direction of the displacement of the eyeball is determined by the location of the metastases within the orbit. Expansive metastases of the bony wall of the orbit, usually retrobulbar, will lead to a propulsion of the eyeball. Metastases at the top of the orbit, intraconal, will result in a straightforward propulsion.

Metastases in the ocular muscles have also reported. They will result in uncommon types of paralyses of the eyeball, sometimes complicated by an exophthalmos.
The Claude-Bernard-Horner syndrome is another pathology that can involve an eye in metastatic breast cancer. This is nearly always due to cervical lymph nodes invading the cervical orthosympathic chain.
Enophthalmia, which is part of this syndrome can also be caused, though rarely, by an intra-orbital metastases.

The diagnostic steps involve first an adequate ophthalmological consult, including a fundus examination. An adequate imaging technique should be prescribed. CT is the first line and most adequate for this region. However, the orbit as well as the brain should be included in the study.

Metastases to the Bone

The high incidence of bone metastases from breast cancer is well known. When these occur in the H&N region, the symptoms are initially relatively vague, not always permitting to establish a diagnosis at once, especially when the skeletal metastases are not yet known in this patient.

Pain in the neck, the shoulder or/and the arm can be the first signs of metastases in the cervical spine. The pain can sometimes bedismissed as a neck pain, as we once encountered in a patient, where a osteolytic zone was only detected by CT and located in the processus spinosus of the 4rd cervical vertebra.
Skeletal metastases are usually osteolytic and located at the body or the pediculus of the vertebra, leading progressively to instability of the spinal column and narrowing the intervertebral spaces with compression of the nerve roots. The clinical result is a radicular cervico-brachialgia.
Occipital pain accompanied by painful movement and hindrance of the cervical column or/and the head may be caused by a metastatic lesion in C1-C2. Radiology and scintigraphy (profile image!) may demonstrate a lesion, but a CT will show it more accurately.
Recently, we had a patient in whom the CT image disclosed a heavily pronounced arthrotic deformation, ruling out a metastasis in this patient formerly treated for a breast cancer.

According to the literature (Lally et al.), metastases in the cervical spine accounts up to only 7% of the vertebral metastases. Cumming et al. have calculated on the base of scintigraphic images that the frequency is 6 times lower than in the thoracic vertebrae (fig.8.19). Metastases in the first cervical vertebrae are probably less frequent. It seems, however, that if the imaging procedure is diligently applied, the frequency will be higher.

Nottebaert et al. have given a figure of 27% of cervical metastases, when radiology and scintigraphy were combined with CT. Scintigraphy has, moreover, a low efficiency for the cervical column, but profile imagesshould always be made.
Lally et al. described 6 patients with cervical metastases. In daily practice, they are, however, not so unusual. Bonneville et al. have demonstrated that a diligent examination will show the incidence of metastases in the cervical spine to be rather high. They found metastases in 30 patients or 60% of 50 patients with skeletal metastases, mostly from breast cancer, with five percent in the condyli of the atlanto-occipital joint, 33% in C1 and 62% in C2. Of all these 30 patients 20 had no complaints at all!. We can conclude that metastases are certainly far more frequent than clinical examination would suggest or than the complaints of the patient would indicate, when looked for with by an adequately performed imaging method.

According to the literature, breast cancer is a frequent primary for temporal bone metastases (pars squamosa) (Nelson et al.), but also to petrous and occipital bone (Greenberg et al.).
They rarely solitary, within a clinical picture of diffuse cranial or other bone metastases (Chapter 7).
Progressive hearing loss and left otalgia with recent aural bleeding occurred 8 years after surgery for a T1 ductal adenocarcinoma. A swelling in the external auditory canal was seen and at CT no bone involvement was noted. Biopsy confirmed the metastatic nature (Cumberworth et al.).
Previously, Feinmesser et al. have reported on a F68 where discharge from the left ear lead to the diagnosis of metastasis in the temporal bone, almost simultaneously with the diagnosis of a left breast cancer (no further data). A similar case (F37) had been reported by Shapoory.

Symptomatology of these locations can be somewhat complicated, mostly combining pain with any of the following neurological problems (Greenberg et al.):

- the orbital syndrome, with supra-orbital headache, visual defects, proptosis and some other ophthalmoplegias,
- the parasellar syndrome, with frontal headache, eye paresias without proptosis, always a diplopia, sometimes hypoesthesia of the forehead and also papilledema;
- a middle fossa syndrome (ganglion of Gasser) with functional deficits of V2 and V3, less frequently V1, trigeminal neuralgia and/or hypo- or paresthesias, sometimes accompanied by diplopia, headache, dysarthria and dysphagia;
- the foramen jugulare syndrome combining hoarseness and/or dysphagia, neck pain and a functional deficit of IX, X, and XI (paresia and atrophy of the neck muscles), a paresia and atrophy of the tongue, less frequently the Horner-syndrome and a diminution of acoustic perception, demonstrating an invasion of the petrous bone;
- the occipital condylus syndrome, with significant pain at head movements, dysarthria, dysphagia (tongue!), muscular contracture in the neck and always a paralysis of XII (tongue side-deviation).

Another not so uncommon symptom is a hypo- or anesthesia of the chin (numb chin syndrome) (Harris et al. and others) (see Chapter 7). Mammary carcinoma is responsible for about 64% of the oncology patients with this symptom. The patient reports an anesthesia at the lower lip and chin, sharply delineated to some extent laterally from the midline. Osteolysis of the horizontal part of the mandible is almost always present, with compression of the mental nerve. This is usually confirmed by imaging methods, but sometimes it is so minute that is not visualized. The cause may be also located at the base of the skull, with compression of the trigeminal nerve. In that situation, however, the teeth will also be anesthesized. This

symptom can be very cumbersome for the patient, because of the hindrance it poses for talking and eating, but also for the ongoing unpleasant sensation. Osteolytic metastases in the condyli of the mandible have been reported (Mace et al.).

Metastases in the calvarian bones have the symptoms of local or regional pain, but they are frequently silent even when the osteolytic lesion is relatively extended. Remarkable is the fact that these metastatic locations always respect the dura mater during their further expansion, and do not invade the brain (Hornig). Clinically, the pain of this localisation can be relatively easily differentiated from the headache pain caused by cerebral metastases.

Distribution Pattern of Bone Metastases

Although there are several hundreds of articles concerning the different aspects of bone metastases in breast cancer, only a few give adequate and pertinent pathological or anatomical data.
From the scintigraphy obtained in 55 patients, Cumming et al. reported the distribution at each vertebra. The highest number would seem to be located at the lower half of the thoracic column (fig.8.21). This is at variance of the distribution obtained in prostatic cancer (see further fig. 11.15), where the highest number is observed at the lower parts of the spine.
Other data based on classic radiology were reported by Heller et al. on 58 patients (table 8.104). They found that the radiological aspect was osteolytic in 67.2%, osteosclerotic in 12.1% and mixed in 20.7%.

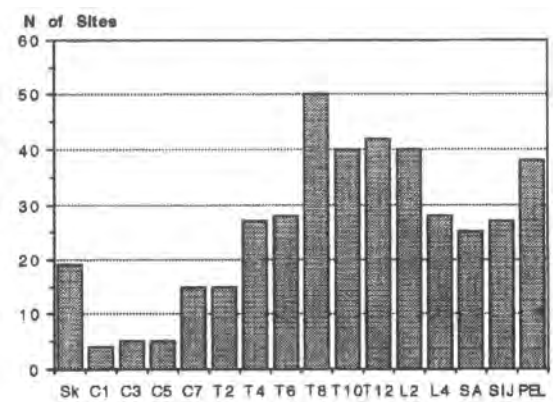

Fig.8.21 - Frequency of bone metastases within the various vertebrae (N=55). Drawn from data of Cumming et al.

Metastatic disease in breast cancer can be confined and unique, at least as a first recurrence, to the bone. This has been addressed by Sherry et al., who remarked this in 86 or 21% of the group of 544 patients with BC (with bone metastases?). The median age of the concerned patients was 52 years (range (30-72 years). Within a mean time of 24 months, however, 42% of these patients developed other visceral metastases.
On the other hand, they retrieved from a review of 410 patients with metastatic BC, 15 patients or 3.6% with bone metastases at initial diagnosis. The mean age was 63 years (range 41-87 years).

Table 8. 104 - Breast Cancer
Distribution of Bone Metastases (N=58)
Data of Heller et al.

Site	Percent	Site	Percent
Skull	8.8%	Femur	10.0%
Clavicula - Ribs	12.2	Patella	0.3
Arm Prox.	5.1	Tibia	0.32
Cervical spine	9.5	Foot	0.1
Thoracal spine	24.4	Scapula	0.8
Lumbar Spine	13.7	Mandible	0.5
Pelvis	14.2	Sternum	0.1

Interesting data were reported by Galasko et al. Of 963 successive patients, 52% died within 7 years. Bone pain was observed in 420 patients, but in only 207 or 21% were bone metastases proven. Another literature report cited by the authors mentions that bone metastases were found in 17% of 269 patients. They counted 82 structural bone site destruction, of whom 52 were in the spine with 11 compressing the cord.

It is most probable that in the patients with bone metastases only, the metastaseis found their way along the Batson's pathway. Some interesting observations were made by Yamashita et al. on a group of 82 patients with bone metastases. They divided the patients in three groups and found some differences in the presence of other visceral metastases (table 8.105). The number of visceral metastases was much higher (significantly) in group B and C, though accurate data were not provided.

Table 8.105 - Breast Cancer
Bone and Visceral Metastases (N=80)
Data of Yamashita et al.

Group	N	M/scan	Viscer.M.
A. Above LumboSacral	46	3.7	17 (61%)
B. Below Lumbosacral	6	1.3	no data
C. Both	30	8.1	no data

They hypothesize that the mode of bone metastases in the uppar half of the body differs from the caudal distribution in bone-only metastases from BC. The lower the bone metastases, the higher the risk of simultaneous or subsequent visceral metastases.
Compared with other cancers, metastases in the sternum are apparently more frequent and can be explained by some degree of lymphatic reflux either from the anterior zones of the chest wall, or from the nodes in the anterior mediastinal or from nodes at the internal mammaria interna (see Chapter 7).
Metastases from BC in the extremities or in the hand and foot (acral) have received much less specific attention in the literature, although every oncologist knows that they occur regularly in breast cancer. The literature does not deal extensively with these sites, except for the problem of treatment of the impending

fractures in the long bones.
Osteolysis at the skull base could be a cause of hoarseness by invasion or involvement of the Xth nerve, and of some shoulder and neck muscle paresis by involvement of the XIth nerve. Deviation of the tongue may be caused by any involvement of the XIIth nerve along its course, mostly by metastases in the occipital condyli.

We have collated some unusual cases in a non-exhaustive list in table 8.106, more to demonstrate the large variability that can occur, although other cancers such as liver, kidney and bronchus have also a wide diversity of bone sites.

Table 8. 106 - Breast Cancer
Some non-axial Bone Metastases reported

Author	Pat.	Histol.	Site of Meta	Interval
Hornig1988	F68	Ductal	Skull Calvaria	1 yr
Lally 1977	Six patients with odontoid fracture			
Mace 1977	F54	Hist.?	CondylusMandible	3 yrs
Klenerman '65	F48	Carc.	Patella	6 yrs
Menon 1994	F53	Ductal	Ankle arthritis	3 yrs
Bloom 1992	Two patients: hand+foot acral			
Freedman 1995	F47	Ductal	Calcaneum	11 yrs

Spinal Cord Compression

As already discussed in Chapter 7, spinal cord compression will occur after destabilization of the vertebrae with serious alteration in the spine stability along with modification of the anatomy of the spinal canal. Specific reports of this problemin relation to BC are numerous, but it was again difficult to obtain accurate anatomical data. The most frequent level for compression is the thoracic, 50% in the radiotherapy series of Maranzano et al., and 61% in the series of Harrison et al.

The mean age was 54 years and the mean interval after first treatment of the BC and the occurrence of cord compression was 42 months in the 70 patients of Hill et al. It was 28 months before the onset of bone metastases, leading to a mean time of about 1 year to the cord compression.

Table 8. 107 - Breast Cancer
Symptomatology in Spinal Cord Compression
(N=70) Data of Hill et al.

		Duration	
Symptom	%	<1week	>1week
Pain	94%	15%	85%
Motor weakness	96	49	51
Sensory loss	79	50	50
Sphincter Probl.	61	84	16
Any except pain	97	35	65
At least one sympt	100	9	91

Symptomatology will not be discussed at length here as it has been extensively discussed in Chapter 7. The data of Hill et al. are interesting as they provide some data according to the time that has elapsed between first sign and diagnosis (table 8.107).
While pain is the most frequent symptom overall, sphincter dysfunction is apparently an important early signal of an impending cord compression.

Bone Marrow Metastases

Bone metastases start with invasion of the marrow by the malignant cells. It is difficult to demonstrate this step demonstration of this step and can, in fact, only be done by bone marrow cytology, an invasive procedure. Moreover, it is not particularly easy to detect single cells within the obtained smears or biopsies and several immuno-histochemical procedures have been studied. This will not be discussed here.
When the bone marrow invasion is somewhat more pronounced it can be visualized by imaging methods such as radionuclide (nanocolloids) scintigraphy or the more expensive MRI. Several authors have reported on the results of bone marrow studies obtained by multiple biopsies during first surgery. The conclusions are far from uniform (table 8.108).

Bone marrow studies are usually performed in the iliac crest, not a common place for bone metastases in BC. Because of the risk involved, it is difficult to select one or more vertebrae. The results of BM-studies are difficult to extrapolate, although one can assume that when cells are present in the bone marrow cells, they are probably everywhere. Unlike bone biopsy, bone marrow cytology should allow the detection of disseminated tumor cells by any immunohistochemical methods. It should be stressed, however, as Solomayer et al. have discussed, that bone marrow cells should not be confused with metastases or micrometastases, but only considered as an indicator of potential dissemination. It is well known that only a few circulating cells will develop or cause a metastasis.

Metastases to the Central Nervous System

Metastases to the central nervous system are not uncommon in the evolution of mammary cancer. Like most of the other metastatic localisations, their frequency diminishes with age. This has been shown in clinical and in autopsy series (fig.8.16).
Brain metastases will occur in about 10% of all patients with mammary cancers. Of 100 brain metastases, 20% are from breast cancer patients. Kiricuta mentions that 60% of the first diagnosed metastases in the evolution of a breast cancer, are situated in the brain. Boogerd has a lower figure of 35%. Compared with brain metastases from other primaries, metastases of the breast cancer remain rather small in volume.

Table 8.108 - Bone Marrow Studies in Breast Cancer
Selected Reports and their Conclusions

Author	Result	Conclusion of the study
Kamby 1987	N=380 at first Recurrence Positive in 87 (26%) Xray positive in 78% of the (+) and 16% of the (-)	Bone marrow is the primary site of metastatic bone disease
Kirk 1990	N=25 To-T2NoN1Mo Positive in 12 (48%)	No correlation with subsequent evolution
Diel 1990	N=128 'operable' patients Positive in 41 (32%) overall	Positivity correlates with T, but not with N or ER At 24 months: 45% of (+) had bone metastases 11% of (-) had bone metastases Shorter relapse free interval in (+) : 8 vs.15 mo Conclusion: study of bone marrow is useful
Cote 1991	N=49 Stage I-II Positive in 18 (37%)	Recurrence at 2 yr : 33%M of (+), 3% of (-)
Diel 1992	N= 260 M0-patients Positive in 115 (44%)	Suggestion of good predictive value for all distant relapse
Harbeck 1994	N=100 M0-patients Positive in 38 (38%)	BM(+) is a statistically significant prognostic factor for early relapse, certainly for bone metastases
Diel 1996	N=727 'operable' patients Ax. Lymph Node neg : 31% Ax. Lymph Node pos : 55%	Aspiration immediately after surgery Positivity correlates with T, lymph node, grade Strong prognostic factor in T < 2 cm.
Molino 1997	N=109 Stage I-II Positive in 34 (31%)	Found only excess positive during surgery No association with T, N, ER or menopausal status No data on follow-up
Solomayer 1998	N= 1465 biopsy positive in 1.7%	Procedure not to be recommended See text

Table 8.109 - Breast Cancer
CNS Metastases - Site Distribution (N=309)
Data of Tsukada et al.

	All N=309	Single N=81	Clinical(') N=96
Cerebral grey	40%		57%
Cerebral white	36	3.5%	45
Cerebellar grey	28		42
Cerebellar white	24	2.2	39%
Pons	7	1.5	15
Medulla	4	0.6	5
Pineal gland	5	0.6	5
Choroid plexus	3	0.5	5
Other brain sites	8	0.4	7
Cranial dura	54	--	51
Leptomeninges	19	--	33
Spinal cord/dura	10	--	20
Total :	**737 sites**	**7.8%**	

(') before CT-era

A very detailed study on the distribution of metastases within the CNS on 309 patients with CNS-metastases (193 with brain) was published by Tsukuda et al., from a series of 1,044 breast cancer patient (table 8.109). This result in an incidence of CNS-metastases at autopsy of 29% for CNS and 18.4% for brain metastases.

These data show that 62% of the patients with CNS-metastases had intracranial locations, but 73% when in the group of clinical diagnosed metastases, pointing to the difficulties in diagnosis for extra-cerebral CNS locations.

Another series was reported by Kiricuta et al. From 795 breast cancer patients coming to autopsy, 287 were found to have metastases and 62 with CNS-metastases or 7.8% of all and 21.6% of the patients with metastases (table 8.110). In their series, 54% of the patients were younger than 55 years.

From a surgically treated (selected cases) series of 70 patients, we could retrieve some data on site distribution (table 8. 111).

Table 8.110 - Breast Cancer
CNS-Metastases - Site Distribution (N=62)
Data of Kiricuta et al.

Site		Appearance as	
Cerebrum	58.0%	First recurr.	61.3%
Cerebellum	16.1	Second	24.2
Brain stem	3.2	Third	8.0
Spinal Cord	1.6	Fourth	6.4
Nervus Opticus	3.2		
Not specified	17.1		

Table 8. 111 - Breast Cancer
CNS Metastases - Site Distribution (N=70)
Data of Wronski et al.

Interval first diagnosis - metastases within 28 months in 50%
Hemisphere concerned
Bilateral 8.5%, Right 48.5%, Left 40%
Location : 83%
Tumor Diameter : 50% less than 4 cm
Single :77% (selected series)
Meningeal involvement : 23%

In the (non-surgical) series of Lentzsch et al., only 30% had single metastases and in 16% of the patients with brain metastases there were no other metastases, stressing that brain metastases are usually part of widespread disease. To our knowledge, data on the distribution within the brain, even for single metastases have not been reported.
Interesting data and conclusions have been reported by Dethy et al. in a study of 89 patients with CNS-metastases. In 52% of the cases, brain metastases appeared in the context of progressive disease with systemic metastases and step-by-step hematogenous dissemination. In the second group of patients (24%) the metastases appeared while disease outside the brain is under control, most probably because the brain is protected for the chemotherapy-drugs by the blood-brain barrier. In the third group, brain metastases are the first relapse (20%), as they were probably present at first diagnosis and treatment.

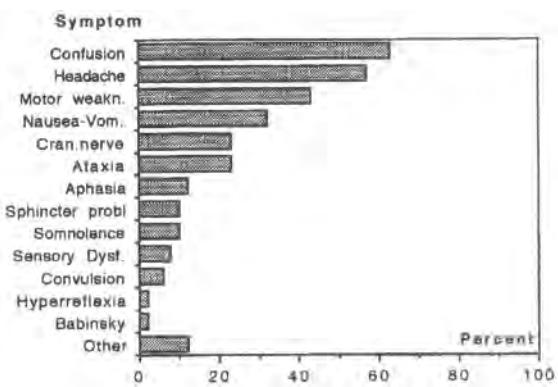

Fig.8.22 - Frequency of clinical symptoms at diagnosis of brain metastases of breast cancer in 50 patients (drawn from data of Dethy et al.)

Symptomatology

The symptomatology of brain or CNS metastases is no different in breast cancer patients to other primaries, as was discussed in Chapter 5. A good overview has been provided by Dethy for brain metastases (fig. 8.22), and for patients with epidural metastases (fig.8.23).
The classical syndrome of headache, neurologic deficits and vomiting is not always present. There may be more of these symptoms and clinical signs. Any symptom can also be absent, but instead, changes in mood and behavior may occur. Hemiplegia and coordination disturbances may be first sign of cerebellar metastases.

Mammary carcinoma is the primary of only 10% of the cerebellar metastases, bronchial carcinoma having a much higher rate, as much as 66%. The clinical picture is dominated by coordination deficits.

Peripheral neurological deficits are not frequently first symptom. They mainly occur when metastases are situated in the strategic Rolandic zone or in the base of the skull.

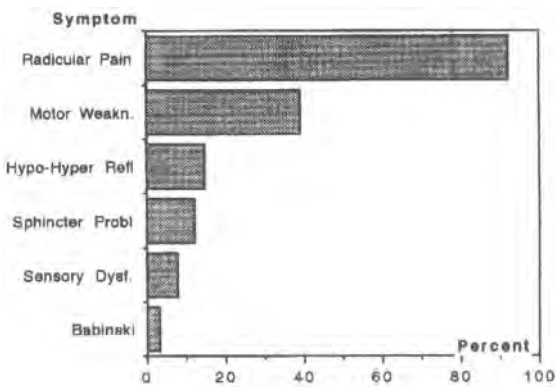

Fig.8.23 - Frequency of clinical symptoms at diagnosis of epidural metastases of breast cancer in 39 patients (drawn from data of Dethy et al.)

Hunter et al., in their review of metastases in the brain stem, found that mammary carcinoma is the primary for only 13.5% of these metastases, whereas bronchial cancer accounts for up to 34%.
Sometimes isolated metastases can be at unusual places, whereby a single cranial nerve deficit occurs. It as has been reported for an isolated hypoglossus palsy with atrophy of the tongue. More complex cranial nerve deficits can also occur.

Neurological examination and imaging methods are the cornerstones of the diagnosis.
At the beginning, the diagnosis can be difficult, but the present possibilities of computer tomography will allow an earlier diagnosis. Isotope scintigraphy has been abandoned, although a few cases have been reported where CT was silent, but the metastasis was revealed by scintigraphy. It is worth mentioning that at CT of the brain, Shi et al. detected primary brain tumors in 6 of the 304 breast cancer patients.

Leptomeningeal Carcinomatosis

Metastatic spread to the meninges is not uncommon in breast cancer. From the data of Tsukada et al., it is observed in 10 to 30% of the patients with CNS metastases from a breast cancer.
Its symptomatology has been discussed extensively in

Chapter 5, none being specific for breast cancer (Yap et al.).

A very rare presentation is LM as initial or first manifestation of breast cancer. Contrary to other primaries, this is very rarely reported for BC. In the large series on CSF-cytology as of Bigner et al. no such case was included in the 'unknown'-group. Heimann et al. reported on one patient and found one other in the literature.

Meningeal metastases can cause headache, meningism and various other symptoms depending on the location and the extension of the meningeal invasion. Cranial nerve deficits are relatively common in this situation.
One particular aspect that has become overt in the last decades, is the prominent presence of lobular histology in this type of spread, more than the normal frequency.
We have collated some data in table 8.112. that show that almost half of the patients with LM have the lobular histology. Histology is not reported in most of the series concerning this type of metastases. Lamovec et al. observed that cerebral metastases were only of the ductal type. Previously, Smith et al. observed that 9/10 patients with LM had a lobular cancer. More data of Smith et al. are in table 8.113.

Table 8.112 - Breast Cancer
Histology and Leptomeningeal Carcinomatosis

Author	N	with CNS	with LM	%Lobul
Smith 1985		--	2.7%	9/10
Lamovec 1991	261	41-18.1%	6	3 (50%)
Jayson 1994	--		35	58%
Fizazi 1996	--		68	49%

Table 8. 113 - Breast Cancer
Involvement of Central Nervous System (N=29)
Data of Smith et al.

Feature	Meningeal N=10	Parenchymal N=19
Mean age	51 yrs (33-72)	55 yrs (46-59)
Premenopausal	40%	26%
Duct type	1/10	18/19
Lobular type	9/10	1/19
Duration before D.	54 wks (8-120)	24(0-81)
Bone metastases	10/10	26%
Abdomen metast	60%	none

Metastases to the Spinal Canal

As outlined in Chapter 5, several unusual types of metastases within the CNS can occur. First the rare intramedullary metastasis. They have been reported for BC. Stranjalis et al. had one patient and found two others in the literature.
The spinal subdural location is more frequent (Hirsh et al.). They reported on one patient and retrieved 4 other from the literature. Almost all were located at the cervical level, with one at the mid-thoracic. Two other patients (F56 and F52) were reported by Feiring et al.
West et al. have reported on a patient (F74) with a metastasis in the subarachnoid space at the cauda equina, as having apparently derived from an intraventricular metastasis and spread by the CSF.
Several BC-patients have been reported as having (chronic) subdural metastatic hematoma (Jamjoon et al.).
A few cases of a solitary metastasis within the trigeminal nerve have been reported, both mimicking trigeminal neurinoma and presenting with neuralgia (Nakano et al.; Hirota et al.).
Metastatic breast cancer presenting as a cavernous sinus syndrome is also rare (Ryan et al.).

In the neck, compression of the cervical plexus can cause pain in the neck and/or occipital region, but could also involve the nervus phrenicus causing hiccup. Lymph node or any other metastase lower in the neck could cause the above mentioned Claude-Bernard Horner Syndrome (CHB).

Headache is a common symptom, of variable intensity and location, depending on the anatomical location and extent of the intradural metastases. It has to be differentiated from skeletal metastases, occurring in the face bones or in the cervical column.

Hoarseness is a frequent symptom in the evolution of mammary carcinoma. It seems to occur in about 1% of all patients with breast cancer. Westbrook et al. noted hoarseness in 32 of 3,000 patients. In about 70% of the cases, it was due to a mediastinal involvement of the nervus recurrens, the remaining being caused by cervical lymph nodes. In some of these patients, the clinical picture was complicated by a phrenicus palsy and/or CBH syndrome.
Similar to the compression is the symptomatology caused by spinal epidural or extradural metastases. This problem has scarcely been addressed in the literature, except in an extended report by Boogerd et al. concerning 100 patients with epidural metastases as seen on myelograms. While almost all patients had bone metastases, the epidural metastases were not necessarily caused by these metastases but through separate metastases within the spinal canal, even at multiple sites. The majority of the asymptomatic blocks were in the thoracic area, but overall the symptomatic were most frequent in the lumbosacral region, mostly at L4. Symptomatology is difficult to distinguish from compression, but radiology will separate them clearly.

Metastases to the Endocrine Organs

delaMonte et al. designated as the primary endocrine organs those structures traditionally regarded as having a pure endocrine function: the anterior pituitary, the thyroid, the parathyroids and the adrenal cortex. The secondary endocrine organs are the posterior pituitary, the pineal gland, the thymus, the adrenal medulla and

Table 8. 114 - Breast Cancer : Metastases in Endocrine Organs
Review of Literature on Autopsy Data (type 4 metastases)

Organ	Abrams 1950 N=167	Sproul 1971 N=100	Meissner 1971 N=432	Viadana 1973 N=647	Cifuentes 1979 N=141	Cho 1980 N=707	Hagemeister 1980 N= 166	Amer 1982 N= 368	delaMonte 1984 N=187	Parham 1989 N=85
Pituitary	9%	--	--	20%	17%	--	6%	--	15%(')	--
Parathyroid	--	--	--	--	4%	--	--	--	6%	--
Thyroid	5%	24%	8%	20%	20%	--	12%	19%	20%	--
Adrenal	54%	49%	34%	38%	41%	36%	30%	43%	C.43% M.38%	5%
Ovary	23%	20%	12%	15%	21%	15%	21%(')	--	29%	1%
Thymus	---	--	--	--	--	11%	--	--	16%	--
Pineal Gland	---	--	--	--	--	--	--	--	2%	--

(') : 6% intra-operatively.

Table 8.115 - Breast Cancer - Influence of histology type on the incidence of metastases in endocrine organs (all autopsy data).

Organ	Harris 1984 Ductul N=76	Lobul. N=14		Lamovec 1991 Ductul. N=195	Lobul. N=25	Bumpers 1993 Ductul. N=86	Lobul. N=32
Adrenal	22%	36%	N.S.	23.2%	44%	35	62.5
Pituitary	--	--		--	--	16	50
Thyroid	---	---		7.2	12	21	37.5
Ovary	2.6	36	p<0.002	11.3	52	8	37.5
Parathyroid	--	--		--	--	4.7	25

the ovaries. They are not strictly or solely endocrine organs. This classification should probably be regarded as artificial.

Autopsy statistics - with type 4 metastases - show that of all endocrine organs, the adrenals are the most frequently involved, in up to 54% of all examined patients. Metastases in the ovary and thyroid account for about 20%, while metastases in the other endocrine organs are much less frequent or even rarely reported (table 8.114). In 187 patients, dela Monte et al. disclosed a similar amount of relative data after a seemingly very diligent autopsy study (table 8.115).

delaMonte et al. have differentiated between both partsof the adrenals and of the pituitary, but no significant difference was found. They noted that 52% of the patients had a single primary endocrine organ metastasis, 21% had metastases in two 'endocrine' sites, 22% in three sites and 5% in all primary endocrine organs. They found also some correlation with non-endocrine organs.

Thyroid and parathyroid metastases correlated with pituitary, adrenal cortex and ovary, but also with heart and lungs. Adrenocortical metastases correlated highly with other endocrine organs and with liver, spleen, kidney, bone and serosal surface metastases. Heart and liver metastases correlated with the pituitary. Metastases in the endocrine organ occur usually in a setting of widespread metastases, at least as far as autopsy data are concerned (delaMonte et al.).

The incidence of metastases in various sites is low unless 3 major sites, namely the liver, the lungs and bone, are involved. When the liver is involved, the incidence of ovarian metastases sharply increases. The same happens for the pituitary when bone is involved, and for the adrenals when liver and bones are committed (Viadana et al.).

Influence of the Histology Type.

A substantial difference was noted for metastases in endocrine organswhen lobular carcinoma was compared to ductal carcinoma. There were more, but not significantly, adrenal metastases, but significantly more ovarian metastases, about 14 times.

Comparing the autopsy reports in 25 ILC and 195 IDC, no significant differences was found between adrenal or thyroidal metastases, but a highly significant difference in ovarian metastases at a $p<10^{-6}$. No other endocrine organs were studied in the report by Lamovec et al. More recently, Bumpers et al. compared the metastatic pattern in endocrine organs for lobular carcinoma in 32 patients at autopsy. The relative frequency of endocrine organ involvement is higher for lobular carcinoma (p=0.016), but the pattern is indeed the same. They found a significantly higher incidence of ovarian metastases, but also a higher incidence for the pituitary and the less frequently studied parathyroid glands. The pattern of multiple endocrine organ metastases is significantly different (table 8.115).

The significance of the differences between both histologies is unknown. Prospective evaluation could reveal some facts, but the low clinical impact of metastases in these organs and the difficulty in imaging them probably precludes any worthwhile conclusion.

Metastases to the Pineal Gland.

Metastases in the pineal gland are uncommon. The reason may be that they are probably clinically asymptomatic and that they are not systematically looked for at autopsy. The exact incidence is unknown. A computer tomography study will show the lesion, but the nature of the metastases within the pineal gland is probably not easy to prove on radiological grounds. Indeed, most of the cases concerned an elarged pineal body revealing its metastatic nature and were autopsy findings. Only type 4 metastases are reported in the literature.
The most frequent primary tumors as primaries for pineal metastases are breast and bronchial cancer. A literature survey in 1966 by Ouyang et al. found 24 cases, of which 9 (37.5%) were from a breast cancer.
Kerenyi et al. surveyed the literature in 1994 and collected 74 cases, of which 23 were from breast cancer (32%), including 3 cases of their own. They disclosed 3 pineal metastases (age 46-71 years) or 11% of their autopsy studies of their own 27 autopsy cases (age range 37 - 87 years). Although pineal gland metastases are stated to be rare, 11% is not a low figure !
They could observe that destruction of the pineal gland parenchyma clearly accelerated the progress of the other metastases, resulting in a shorter survival time when compared with those patients without pineal metastases. There was an infrequent association with metastases in the pituitary. We are not aware of other clinical or autopsy studies on pineal metastases in breast cancer, except delaMonte et al. mentioning 3 in 187 or 2%.
Apparently, metastases in the pineal gland rarely cause any symptoms, unless a certain volume is reached. Moreover, it would appear that as many other intracranial metastases are often present, this location might be overooked.

Metastases to the Pituitary

Mammary carcinoma has a particular propensity to metastasize in the pituitary. About 70% of these are located in the posterior lobe, causing the well-known diabetes insipidus, accompanied by excessive polyuria and thirst. Clinically it must then be differentiated from the other oncological causes of thirst such as hypercalcemia.

In 14% of diabetes insipidus cases, a metastasis is the cause. Breast cancer forms 60 to 70% of all these, although not all will present the clinical symptoms. It should be mentioned that in man bronchial carcinoma is the most frequent primary cause. These metastases are more frequent in women than in men, with a 60/40 ratio. Twenty percent of the pituitary metastases are from a breast cancer (Kimmel et al.). Some authors claim that pituitary metastases never occur without skeletal involvment (Saeger et al.).

Metastases in the pituitary are much more frequent in younger patients. They can occur a long time after diagnosis of the primary. Many are only detected at autopsy (Grisoli et al., Hagerstrand et al.). In the series of Yap et al., of all patients with diabetes insipidus, only 12 (31%) were premenopausal.

In the era when hypophysectomy was performed as an hormonal treatment for metastatic breast cancer, metastases were found in 10% to 20% of the pituitaries examined (Marin et al.).
Any metastasis in the anterior lobe could cause a panhypopituitarism, though this happens only rarely.
The reason for the higher frequency in the posterior lobe is the anatomical architecture of the blood supply: the posterior lobe has a direct arterial arrival, whereas the anterior lobe is supplied after the portal system of the hypothalamus.
When the tumor expands, it may cause some pres-sure on the chiasma opticum, causing the well-known bilateral hemianopsy. This must be differentiated from any skeletal involvement in the region.

MRI is the technique of choice to demonstrate this location and to differentiate it from a hypophyseal adenoma. This last one causes a typical dumb-bell image, because it respects the diaphragm (Chaudhuri et al.).

Grisoli et al. state that in these clinical series the metastases are more frequently located in the adenohypophysis, whereas in autopsy series no difference is seen. Extensive study of the pituitary in breast cancer autopsy patients disclosed metastases in 29% of 125 patients (Marin et al.).
One patient has been reported presenting only hypophyseal and gastric metastases from an inflammatory breast cancer (Ghosn et al.).

Reviewing the literature, we found 36 reported cases of pituitary metastases diagnosed during follow-up. Some are in table 8.116 They occurred at all ages, from 26 to 78 years. As the age of the patient is usually reported when the metastasis is found, we see in the table that 60% of the patients are younger than 60. Visual problems were reported in 8 as the sole presenting symptom. The interval can be very long, up to 27 years, but in half of the patients for which the interval was given it occurred within 2 years after treatment of the primary. Diabetes insipidus was the first symptom in 20 of the 31 sufficiently documented reports.

The relatively high frequency of pituitary metastases could hypothetically be explained by the presence of prolactin, representing a favourable biological soil (Marin et al.).

Table 8. 116 - Breast Cancer
Pituitary metastases during follow-up (N=36)
Literature Review by the author

Author	Year	Age	Interval	Symptom	Author	Year	Age	Interval	Symptom
Houck	1970	54	11 yrs	DI	Kimmel	1983	66	2 yrs	no DI (')
		??	18 yrs	DI			57	1 yr	no DI (')
		70	7 yrs	DI	Branch	1987	??	NG	NG
		31	1 yr	DI	Nelson	1987	57	27 yrs	ophth.probl.
		54	6 yrs	DI	DeLattre	1990	64	7 mo	DI
		63	NG	DI	Chiang	1990	47	5 yrs	headac-vision
Teears	1975	38	13 mo	DI	Mayr	1993	76	18 mos	NG
		44	1 mo	DI			35	20 mos	NG
		46	4 mo	DI-aphasia			46	2 yrs	NG
		49	4 yrs	DI+ophth.probl.	Schubiger	1992	52	NG	DI
Kistler	1975	71	2 yrs	bit.headache			54	NG	DI
		48	NG	NG			37	NG	DI
Cox	1979	36	5 yrs	bil.headache	Aabergh	1995	68	4 yrs	ophth.probl.
Steimle	1983	61	14 mo	bil.blindness	CarsinNicol	1995	48	2 yrs	DI + neurol.
Kimmel	1983	70	NG	DI+ophth.probl.			42	6 yrs	DI
		56	8 yrs	no DI (')			65	2 yrs	DI
		70	2 yrs	no DI (')			41	4 yrs	DI
		69	5 yrs	no DI (')	Sioutos	1996	26	36 mo	DI-Blind-Epil.

DI: Diabetes Insipidus; NG : no data (') no further data ophth.probl.: ophthalmic problems; neurol.: neurologic; bil.:bilateral.

Metastases to the Thyroid Gland.

A painless progressive swelling within a lobe of the thyroid may be a metastatic lesion. Further enlargement may lead to hoarseness, dyspnea and even to a C.B.H syndrome.
The clinical diagnosis of a metastasis in the thyroid is not particularly difficult to make, as cytology or a biopsy can confirm the diagnosis. Surgical excision might be preferable. Imaging studies cannot differentiate between primary or secundary tumors, or even with other thyroid pathologies. Ultrasonography is certainly the first-line method for evaluation of the nature of any swelling.

It seems that thyroid metastases are relatively frequent from breast cancer, about 20% of the thyroidal metastases. An autopsy study of 2,050 cancer patients disclosed 188 thyroidal metastases, or 9.2%. Of all these patients, 250 had a breast cancer, with 52 thyroid metastases, a percentage of 21% (delaMonte et al.). A recent literature survey by Reymund corroborates these figures.

Thyroid gland metastases are known to occur frequently in renal carcinoma (Chapter 11), but breast cancer seems responsible for about 20% of the intrathyroid metastases.
A number of cases have been reported where the thyroid mass and metastases preceded the diagnosis of the primary breast cancer. (Ghandhi et al.; Rodier et al.). One case diagnosed simultaneously was reported by Rigaud et al. Accompanying hyperthyroidism was reported in one case (Edmonds et al.).

Many case reports on thyroid gland metastases have been published. From the literature we collected 12 adequately reported cases. The patients were all older than 40 years. The interval between diagnosis of primary and metastases ranged from 0.5 to 16 years, the majority within 6 years. Twenty other cases were found in the literature but buried in larger series, without further details being given.
An autopsy study (Favre et al.) of 2,050 cancer patients disclosed 188 thyroid metastases, or 9.2%. Of the 250 patients with breast cancer 52 had thyroid meta-stases (21%). Similar data were obtained by Reymund et al.

Metastases to the Parathyroid glands

The study of parathyroid gland metastases is rather difficult unless the thyroid gland and its immediate vicinity is microscopically serially studied. Systematic studies on that site are almost non-existant. Only type 4 metastasis have been reported.
In 1972, at the Memorial Hospital Horwitz et al. performed a systematic autopsy study of the PT gland in 160 cancer patients. Involvement was found in 19 patients, resulting in an incidence of 11.9%. Nine of the 19 (47%) were from a breast carcinoma. The metastatic involvement concerned at least one of the parathyroids, though in 3 patients all four glands were involved. Examining the autopsy protocols performed at the same hospital before their prospective study, they found an incidence of 5.3%, of which 37% (15/40) were from a breast cancer primary. The total number of breast cancer coming to autopsy wa,s however, not stated.

In the retrospective series, osteoblastic metastases were found in 7 of the 15 (46%) of the breast carcinoma pa-

tients and in the prospective series 4 of the 9 (44%). As this type of skeletal metastases is relatively uncommon, there must be some relationship. Hortobagyi has quoted indeed that in all breast cancer patients, only 12% of the bone metastases are osteoblastic.
Extensive replacement of parathyroid tissue can lead to hypocalcemia. This is, however, very rare. To what extent it can be related to any case of the more common hypercalcemia is unknown.
The above mentioned study of delaMonte et al. showed parathyroidal involvement in 6% (12/187) of the breast cancer patients. No difference according to age was noted. For lobular carcinoma, the incidence would seem rather high, according to Bumpers et al. They found an incidence of 25% (8/32), significantly higher than in patients with ductal carcinoma, only 4.7% (4/86). In another large series of 707 patients, Cifuentes et al. found metastases in the parathyroid in 4%. Widespread metastases were present in all cases.

Metastases to the Thymus Gland.

Although the thymus gland is not commonly considered an endocrine organ, we thought it worthwhile to include it in this study. Here also, only type 4 metastases have been reported.
Metastases to the thymus are asymptomatic and probably will not be diagnosed as such, in view of the difficulty to differentiate them from mediastinal nodes, even with computer tomography.
The study at autopsy of the thymus is not easy, mostly because of its extreme involution with age. Thymic tissue could be found in only 171 of the 272 patients coming at autopsy in the study of Middleton. The age factor was, howeve,r not examined.

Thymic tissue was found in 102 of the 112 oncology cases. Forty percent (4/10) of breast carcinoma patients had thymic metastases without any other mediastinal involvement. The age of the patients was between 44 and 62. We could not find any other reports on thymic metastases in the literature, up to our knowledge, except one by Cifuentes with 75/707 or 11% and by delaMonte et al. reporting an incidence of 16% (29/187).

Metastases to the Adrenal Glands.

The incidence of metastase in the adrenal has been studied at autopsy, though such studies date back to the era when adrenalectomy was frequently performed as a hormonal treatment for metastatic breast cancer.
There are no reports of clinical symptoms of adrenal metastases revealing breast cancer. Clinical symptoms of adrenal failure due to metastases are rare and become evident only when almost 90% of the adrenal glands is destroyed. Furthermore, as adrenal metastases are usually part of widespread metastases, symptomatology will be related to the dissemination.
True hypo-adrenalism (Addison) with high ACTH and low adrenal hormone levels is very rare. Solitary or bilateral adrenal metastases are hardly ever reported (Davi et al.).
Imaging the metastases in the adrenal has been given extensive coverage in the recent literature. Metastases from breast cancer may be confirmed by a fine-needle aspiration biopsy under CT-guidance.
Incidentaloma studies may well reveal metastases of unknown breast cancer. To our knowledge, Kloos et al. are the only authors who have stated that this incidentalomas ara a rare or not clearly defined occurrence in the literature. Metastases to the adrenal glands presenting as an Addisonian crisis is rare as first symptom or during the follow-up. It is currently documented for bronchial cancer.

Why are such cases rare? Four possible reasons have been proposed by Hill et al. as quoted by Cedermark et al.:

1. The similarity between an Addison crisis and symptoms of disseminated metastatic process.
2. Treatment with glucosteroids is often offered to these patients, masking the hypo-adrenalism eventually present.
3. Diagnostic procedures are often omitted in this situation, possibly precluding the detection of metastasis.
4. The remaining adrenal tissue can hypertrophy to compensate for any even limited destruction.

The incidence of metastases - 30 to 54% - is indeed relatively high, as far as autopsy studies are concerned (table 8.114). The reason is not clear though certain factors could explain it. In the first place the blood supply and the flow rate to the adrenal are relatively high. The adrenal glands receive their blood almost directly from the aorta via the inferior phrenic and the renal arteries. (Lumb et al.). These arteries subdivide into a large number of up to 60 small vessels, to reach the gland. Flint (quoted by Lumb) described a capsular plexus of finely branching and anastomosing arteries, from which various arteries reach the capsule at various depths and end up as arteries in the medulla. In his extensive classical autopsy studies Willis reported that small metastatic emboli most frequently occur in the cortical capillaries.

Some authors have pointed out that the state of the adrenals at autopsy is important for the ifinal evaluation, as the glands rapidly undergo autolysis after death. The difference in cellular aspects between normal and cancerous tissue is not always evident, in view of the cellular morphological variation (Tuaillon et al.). Others have suggested that metastatic implants probably grow well in the adrenal because of the high steroid of the adrenal.
The incidence at autopsy is reported between 20 and 50% (table 8.117). The frequency of adrenal metastases is twice that of ovarian metastases, but the number of thyroid metastases approach the ovarian metastases.

Table 8. 117 - Breast Cancer
Literature review on Adrenal metastases found at Adrenalectomy
Review by Tuaillon et al.

	Year	N	Involvement	
Higgins et al.	1953	56	25%	Literature Review 1953-1958
Taylor	1953	40	55%	191/536 or 35.6%
Cade	1954	25	50	Tuaillon 1963 Own cases : 47/155 or 30.4%
Block	1959	27	44	(Bilateral 22, Right 12, Left 13)
Lumb et al	1959	235	39	
Romieu	1960	28	43	
Aldrete et al.	1967	46	29 Range 25 - 55%	
Fracchia et al.	1967	500	29	
Oberfield et al.	1979	46	45	

When the adrenals were removed operatively for hormonal treatment purposes during the fifties and sixties, the same values were obtained (between 30 and 50%).
Tuaillon describes three types of metastases:

- Massive invasion with glandular, alveolar or tabulated aspects, apparently depending on the zone of the adrenal which is invaded. This is accompanied by large zones of necroses;
- Less extensive invasion, usually with trabecular cords, without necroses and a rare glandular differentiation;
- A not so frequent solitary or small number of micro-nodules, probably the initial event.

In all cases the structure of the adrenal is rearranged with some adenomatous aspects, hemorrhagic or pseudo-adenomatous zones.

The metastases are bilateral in a large number, up to 80% in their cases.
The medulla is the most frequent location, at least in the series of Tuaillon. Aldrete et al. report only 33% and Lumb 40%. The latter author, on the other hand claimed that only the medulla was involved in 20%, but both zones in 60% (table 8.117).
The high frequency of adrenal metastases of breast cancer in comparison with other cancers has also been explained in terms of a preferential tropism possibly indicated by hormones. In postmenopausal women the adrenal is the major source of estrogens, producing androstenedione converted by the aromatase enzyme in peripheral tissue to estrone and estradiol. Estrogens are also directly secreted in small amounts. It has been hypothesized that the adrenal gland would be a good environment for the cells to proliferate (Davi et al.).

Metastases to the Placenta

In asmuch as the placenta is an endocrine organ, we have to consider the incidence of metastases in its ephemeral existence. The incidence is certainly low as women in childbearing age have a relatively low incidence of breast cancer, and breast cancer in pregnancy is not frequent. When it occurs, the histological examination of the placenta is not always performed.
In 1989 Dildy et al. reviewed the literature and found 52 cases, of which 7 or 15% were from a breast cancer. Potter et al. suggested that apart of the low number of pregnancies at risk, cancer may induce abortion, many cases not being reported. In many cases pregnancy is terminated and in most instances of maternal cancer there is no metastatic spread.
Clinical signs are almost absent. In the case of Angate, the placental metastases were only found at pathological examination of the placenta. In cases of extensive involvement it may result in premature delivery or even abortion.
It has been stated that placental metastases from breast cancer do not occur before the third trimester, unlike malignant melanoma (Pfuhl et al.).

Chemotherapy and Endocrine Metastases

Amer et al. reviewed the autopsy records of 368 patients with breast cancer, one third of whom did not receive any chemotherapy, at presentation with metastases. Except for a significantly higher number of CNS-system metastases, they did not find any significant differences in metastatic pattern, nor in the two endocrine organs studied, the thyroid and the adrenal.
The respective incidence of metastases was 20% and 43%, quite alike the data mentioned above.
Other authors have also examined the influence of adjuvant chemotherapy, but the endocrine organs were not specifically studied (Goldhirsch et al.; Noguchi et al.).

Influence of Estrogen-Receptor Status

Several authors have examined the relationship between estrogen receptor and the pattern of metastases during further evolution. It is well known that brain metastases are more common in patients with ER-negative tumors, being most marked for patients treated at stage I (Stewart et al.). The same patients more frequently develop hepatic metastases.
In ER-negative patients, osseous involvement is more frequent. There is no difference for soft-tissue and pleuropulmonal involvement. Data on metastases in the endocrine organs related to the estrogen status,

have not been reported.

Influence of Age on Endocrine Metastases

Several authors have pointed out the fact that metastases are less frequent with increasing age (Basserman et al.) (fig.8.17). Concerning the metastasis in the endocrine organs, only delaMonte et al. have shown that there is a declining trend with age (fig. 8.24).

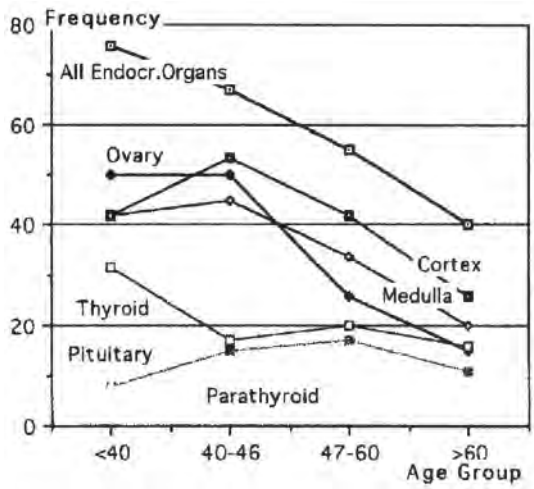

Fig. 8.24 - Breast cancer - Frequency of metastases in endocrine organs depending on age of the patients. Redrawn from delaMonte et al.

Multi-variate analysis has shown that age was an independent predictor for endocrine metastases (delaMonte et al.).In the study of Bumpers et al., all subjects with ILC younger than 50 years had endocrine metastases. On the other hand, if the ages of the patients with pituitary and thyroid metastases is compared, the latter patients (fig.8.25) are definitely older.

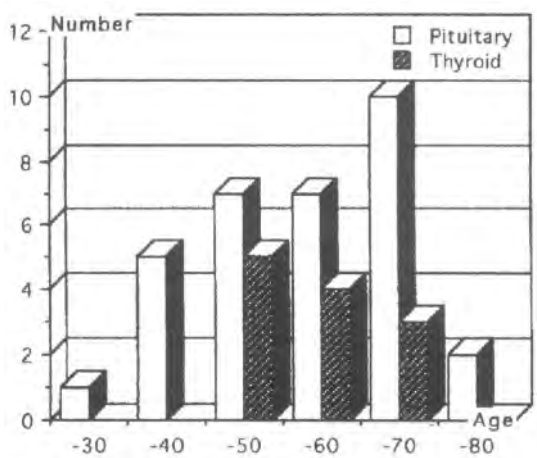

Fig.8.25 - Breast cancer - Age distribution of patients with metastases to the pituitary or thyroid gland. Literature data collected by the author. (from Debois, with permission)

Among the several factors probably implicated in the anatomical location of the metastases and their frequency, age is one, whose effect is as poorly understood as the other factors. Age certainly relates to the biochemical state, influenced by the hormonal and immunological state of the patient. This undoubtedly has an influence on the tumor biology, its aggressiveness and probably on metastatic location.

There is little doubt that the biological behaviour of breast cancer is age-dependent. The metabolic rate, influenced by the function of some endocrine organs, and immunological defences, declines with age. How this affects the implantation of the metastases and their further evolution is, however, a matter for speculation.

TIME LAPSE STUDIES

The incidence and frequency of metastases during the course of follow-up time is almost never addressed. Many studies only report only the mean or the median follow-up time, but this depends precisely on the length of follow-up. Late metastases are indeed not so rare and may influence the data. Sometimes they are even based on mean follow-up time including patients with a follow-up of only a few months.

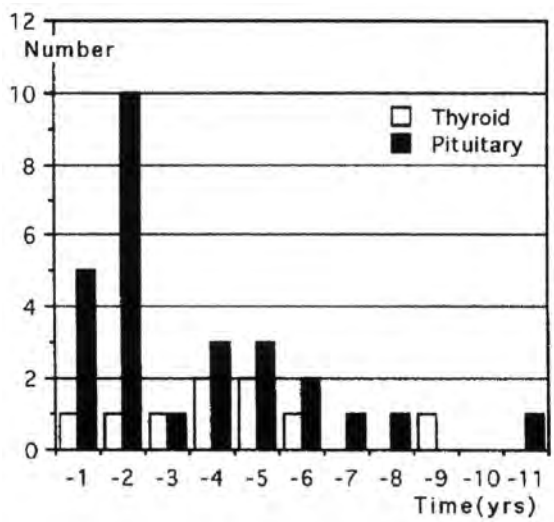

Fig.8.26 - Breast cancer - Number of metastases according to time elapsedafter primary treatment. Literature data on 10 thyroid and 27 pituitary metastases. Review by the author (from Debois, with permission)

From the already mentioned literature data we have seen that the incidence of pituitary metastases is different from the time lapse for thyroid metastases from breast cancer. Pituitary metastases almost all occur within 3 years, whereas thyroid metastases are much more spread in time. This must of course be interpreted with caution, as the literature data could be incomplete (fig.8.26). We are only aware of the study of Pierquin showing two peaks during the follow-up period depending even on the tumor size treated, one

between 3 and 4 years, and another one between 7 and 8 years (fig.8.27).

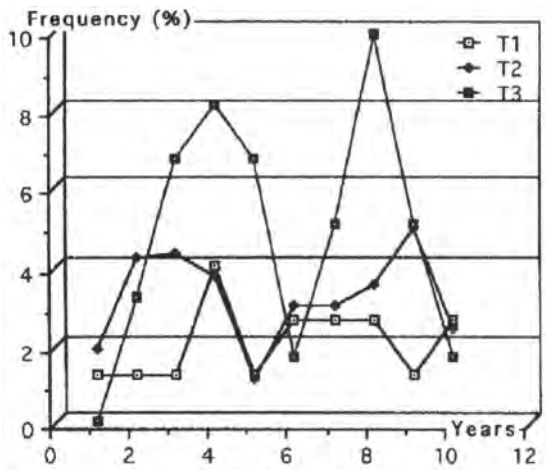

Fig.8.27 - Breast Cancer- Frequency of deaths by metastases in percent for each year of follow-up (Redrawn from data of Pierquin et al.) (from Debois, with permission)

PECULIAR SITUATIONS

It is well known that surgical ablation or medical antihormone therapy with suppression of the hormonal activity of the pituitary, the ovaries or of the adrenals, can lead to a remission of the metastatic process.

One very unusual situation reported is clear clinical remission of metastasized breast cancer occuring spontaneously because of the destruction by a metastasis of the pituitary or the adrenals. Lumb et al. have mentioned, without giving any further detail, that 3 out of their 235 patients, showed clinical remission because of so-called 'auto-adrenalectomy'. Another 3 patients have been reported to present clinical remission due to 'auto-hypophysectomy' (Brugge et al.). These reports date back to 1959 and 1965. We are not aware of reports on similar cases. In view of the fact that almost all patients are treated with hormones or cytostatic drugs, it is possible that such situation will be masked during the clinical evolution.

Clinical and autopsy data clearly indicate a proportionally high frequency of breast cancer metastases within the endocrine organs. Many authors have stated that hormonal environment within these organs may explain this high incidence. The age dependency is a possible factor also because the incidence falls with the progressive decline of the hormonal activity. The age factor however seems also to be implicated in the metastases frequency in other organs. There is no doubtthat this also represents an additional argument for the classical 'seed and soil' theory. Metastatic disease is indeed also related to the intrinsic biology and behaviour of the tumor cells.

Metastases to the Liver

The liver is frequently involved in breast cancer. The literature is replete with articles on the detection possbilities of various diagnostic proocedures, but clear data on its incidence and pathology are lacking, as they are for all organs that are frequently involved.
Reporting on the clinical course of 233 patients with liver metastases, Zinser et al. provided some data. The involved patients were post-menopausal, either natually or after therapy, in 80%. The mean range of disease-free interval was 18 months (0-12 years). Liver metastases were found at diagnosis in 15% of these patients and hepatomegaly (not defined) was present in 50%, ascites in 6% and jaundice in 8%. Both lobes were concerned in two-thirds.
Of 35 patients who underwent hepatic surgery, the lesions were smaller than 3 cm in 28%, smaller than 4 cm in 56%. The lesion was single in 59%, but 12% had more than 5 metastases present (Raab et al.).
There are no data in the literature on the site distribution within the liver.

Metastases to the Pancreas and Bile Tract

Breast cancer seems to rarely metastasize to the pancreas or the bile duct. Many cases will go unnoticed within an eventually widespread abdominal disease, or are not reported.
Obstructive jaundice is a common symptom and will prompt investigations.

Table 8. 118 - Breast Cancer
Metastases to the Pancreas and Bile tract
Cases reported

Author	Patient	Hist.	Sympt.	Interval
Pancreas				
Rabin 1979	F39	Ri.Duct	icterus	1 yr
Azzarelli '82	F49	??.Lob	icterus	4 yrs
Pappo 1991	F52	Le.Lob	icterus	2 yrs
Hardt 1993	F55	??.Duct	icterus	11 mo
Mountney '97	F57	Le.Lob	icterus	2 yrs
Bile tract				
Chang 1978	F64	??Carc	icterus	GB 24 yrs
Rabin 1979	F69	Le.Carc	icterus	GB 2 yrs
Rabin 1979	F46	Ri.Carc	icterus	BD 4 yrs
Hoerder 1983	F52	Le.Carc	jaundice	CD 22 mo
Beaver 1986	F73	Ri.Carc	epig.distress	GB 8 yrs
Franco 1987	F54	Le.Carc	jaundice	HD 6 yrs
Franco 1986	F42	Ri.Ade	jaundice	CD 8 yrs
Pappo 1991	F52	Le.Lob	icterus	GB 2 yrs
Papo 1996	F58	LeDuct	epig.pain	CD 10 yrs
Crawford '96	F66	Ri.Duct	epig.pain	GB 7 yrs
Crawford '96	F57	Ri.Lob	epig.pain	GB 14 yrs
Titus 1997	F50	Le.Duct	pruritus	Vater 4 yrs
Shah 2000	F78	Le.Carc	bile periton	GB sim

GB: gallbladder; BD: bile duct; CD: common duct; HD: hepatic duct; sim: simultaneous

Some cases have been reported as presenting with symptoms of bile obstruction, but obviously without

direct involvement of the bile tract (table 8.118). In these patients, the bile symptomatology was caused by metastatic nodes around the pancreatic head or between the duodenum and pancreas (Engel et al.).

Metastases to the Abdomen

The report of Caskey et al. deserves our attention. 260 breast cancer patients underwent abdominal CT for various reasons, mainly staging. The results are shown in table 8.119 and reveal particular features. Twelve patients had metastases to the stomach, 7 to the peritoneum and 3 to the small bowel.

Table 8.119 - Breast Cancer
Abdominal metastases disclosed at CT (N=260)
Data of Caskey et al.

Finding		Finding	
Ascites	5.4%	Renal metastases	0.4%
Stomachal Meta	4.6	Hydronephrosis	(2)
Peritoneal	2.6	Uterine metast.	0.4
Bowel metastases	1.2	Adrenal	none
Spleen	0.7	Ovary	none
Pancreas	--	Diaphragm	(2)
Lymph node	1.9	Musc.Psoas	(1)

Metastases to the Gastrointestinal Tract

Metastases to the GI-tract are not uncommon. They present under a variable symptomatology, aspecific and easily to confound with the more frequent abdominal or intestinal pathologies. Knowledge of the previous cancer history and a thorough examination of the patient should be sufficient to raise suspicion of a metastatic process.

Three other aspects are noteworthy for this metastatic disease. In the first place, there is the possibility of a long interval between the treatment of the primary tumor and the occurrence of the metastatic disease. Several years, even more than ten, can elapse, with the possibility that the patient will think to be cured of the cancer. A good history and clinical exam can alleviate this.

While ductal carcinoma is the most frequent histology of the primary, lobular histology is the most frequent giving rise to abdominal metastases, in about 60%. Several authors, however, have omitted to provide details in their reports.

Lastly, the diagnosis of a metastatic process will usually only be obtained at surgery, or even at autopsy. Endoscopic biopsies are hampered by the most frequent situation of the non-involvement of the mucosa.

Data on relative incidence according to site have been calculated by Madeya et al. through a literature review. They found 241 reported cases with GIT-involvement with breast cancer (table 8.120). Breast cancer is the second most frequent primary to metastasize to the GIT.

Table 8.120 - Breast Cancer
Involvement of the GIT with metastases
Literature review by Madeya et al.

Esophagus	65 sites
Stomach	80
Small Intestine	18
Appendix	9
Colon- rectum	19

Metastases to the Esophagus

Metastases to the esophagus from breast cancer have only been mentioned in a few cases. In most cases it concerns extrinsic compression, but intramural metastases have also been seen. Confirmatory histology can be difficult to obtain, as the overlying mucosa is not concerned, at least in the earlier phase. The metastatic process is either extrinsic due to mediastinal involvement or intrinsic within the muscularis and submucosa, sparing the mucosa (fig.3.1).

Table 8.121 - Breast Cancer
Esophageal Involvement
Cases Reported

Author	Pat	Side	Site of M	Symptom	Interv
Aubert 1974	F77	Ri.	Lower third	dysphagia	Rev.
Touraine '75	F57	Le	Mid-third	dysphagia	9 yrs
Touraine '75	F52	Le	Mid-third	dysphonia	10 yrs
Touraine '75	F48	Le	Mid-third	dysphagia	12 yrs
Chang 1978	F85	Ri	Mid-third	dysphagia	11 yrs
Chang 1978	F69	Le	Mid-third	hoarseness	1 yr
Biller 1982	F73	Le	Cervical	achalazia	4.5 yrs
Biller 1982	F44	Ri	Cervical	dysphagia	7 yrs
Boccardo '82	F50	Le	Thorac. extrinsic		5yrs
Boccardo '82	F66	Le	Mid-third	dysphagia	9 yrs
Boccardo '82	F49	Le	Mid-third	dysphagia	8 yrs
Boccardo '82	F69	Le	Mid-third	dysphagia	5 yrs
Boccardo '82	F62	Le	Mid-third	dysphagia	7 yrs
Boccardo '82	F55	Le	Mid-third	dysphagia	11 yrs
Bodin 1987	F57	??	Mid-third	dysphagia	5 yrs
Bodin 1987	F56	??	Mid-third	dysphagia	12 yrs
Bodin 1987	F69	??	Mid-third	dysphagia	5 yrs
Taghy 1990	F32	Ri	Cerv-Thor. (extrinsic)		5 yrs
Hastier 1994	F42	??	Low-third	hematemesis	6 yrs
Varanasi '95	F63	Le	Mid-third	dysphagia	8 yrs
Varanasi '95	F64	Le	Mid-third	dysphagia	22 yrs
Varanasi '95	F78	??	Mid-third	dysphagia	8 yrs
Varanasi '95	F67	Ri	Mid-third	dysphagia	22 yrs
Fujii 1997	F68	Le	Mid-third	dysphagia	15 yrs
Maroy 1998	F40	??	Low-third	achalazia	2 yrs

Radiology is rather typical for the extrinsic metastases, most probably from mediastinal peri-tracheal or lower mediastinal nodes. We have observed that CT is almost never mentioned in the case reports, at least in the last decades, so that the actual origin, probably mediastinal metastatic nodes, were not described. In the report of their two cases, Chang et al. made the definite association between a mediastinal nodes and the extrinsic compression. This is usually discussed in the French literature as the 'médiastinite cancéreuse métastatique' (Gouin et al.), in the sense of a lymphatic or loose cellular spread within the mediastinal

tissue.

We have collated the available cases reported (table 8.121). The data show that the large majority of the stenosis is at the mid-third, what can and must be explained by the presence of mediastinal nodes.
Reviewing the literature up to 1990, Madeya et al. observed the following:

- The mean interval between first treatment and diagnosis of esophageal problem was 7.8 years;
- Only 11% of the complaints occurred before the first three years;
- In one-third of the patients, the diagnosis was made later than 10 years after first treatment;
- in 90% the endoscopic appearance was of a normal mucosa;
- a positive biopsy was obtained in only 33%.

In a prospective multi-center study on breast cancer with 91 patients, esophageal comitment was found in 7 or 7.6%.

Metastases to the Stomach

Several cases have been reported with somewhat larger series demonstrating a relatively high incidence, the highest in the whole gastrointestinal tract. A possible pathway is the lymphatic or cellular spread from the mediastinum downwards to the peri-esophageal tissue (see Chapter 3).
There is a significance lack of correlation between the number of stomachal metastases found at autopsy and the number of cases reported, even in relatively large clinical series (table 8.122).
Several reasons can be put forward.
In the first place, a relative large number of patients are asymptomatic, probably because the secondary tumor is not large enough to elicit symptoms. If the intra-abdominal disease is widespread, it might never have been subjected to gastroscopy the diagnostic method par excellence.

The usual relatively large interval between first treatment and the stomachal symptoms might hide the diagnosis and led to the diagnosis of a primary stomachal cancer, although in several instances, the infiltrative lobular histology, the most frequent metastatic breast cancer to the GIT, must be recognized by the pathologist.
The incidence of stomachal metastases has been the subject of conflicting reports. Choi et al. observed an incidence of 8.2% in the 341 autopsied patients and Asch found 6% in 337 autopsies. Previously, figures of 13 and 15% had been reported (Joffe et al).

Clinical symptomatology is either absent or vague and aspecific. In the series of Asch, 14 of the 20 patients with stomachal metastases were only found at autopsy.
Anorexia, vomitus, nausea and epigastric malaise are the most common complaints, and will not always be ascribed to metastatic disease, but will be considered secondary to the various treatments. Hypercalcemia has about the same symptoms. The result is that radiology and/or endoscopy will be done to late or never.

Table 8.122 - Cancer of the Breast
Metastases to the Stomach
Isolated cases reported

Author	Pat	Primary	Symptom	Interval
Klein 1972	F77	Ri.Carc	vomitus	23 yrs
Champault 1982	F65	Le.Duct	anorexia	2 yrs
Walker 1986	F59	Le.Lob.	melena	3 yrs
Walker 1986	F75	Bil.Lob.	epig.pain	nodata
Walker 1986	F48	Bil.Lob.	epig.pain	14 yrs
Casinu 1989	F50	Ri.Lob	nausea	3 yrs
Piquet 1986	F53	Le.Lob	hematemesis	simult
Navarette '89	F51	Ri.Lob	anorexia	2 yrs
Clavien 1990	F49	??.Lob	ascites	2 yrs
Carpentier '92	F68	Le.Lob	ascites	simult
Herrera 1992	F78	Ri.Carc	achalasia	21 yrs
Catino 1992	F54	Ri.Duct	nausea	2 yrs
Melhouf 1992	F35	Le.Duct	anorexia	3 yrs
Benfiguig 1992	F75	Le.Duct	epig.pain	30 yrs
Abboud 1994	F64	Le.Lob	epig.pain	simult
Abboud 1994	F47	Ri.Lob	epig.pain	3 yrs
Abboud 1994	F33	Ri.Carc	perforation	2 mo
Elliott 1995	F58	??.Carc	incidental	4 yrs
Elliott 1995(')	F66	??.Carc	vomitus	3 yrs
Elliott 1995	F61	??.Carc	vomitus	4 yrs
Ostrowski 1996	F52	Ri.Lob	nausea	Reveal
VanTrappen '98	F58	Le.Lob	anorexia	10 yrs
VanTrappen '98	F56	Le.Lob	----	14 yrs
Shimizu 1998	F49	Bil.Carc	anorexia	12 yrs
Lorimier 1998	F63	Le.Lob	dyspepsia	??
Lorimier 1998	F50	??.Lob	epig.pain	5 yrs
Lorimier 1998	F55	Bil.Lob	anorexia	10 yrs
Lorimier 1998	F68	??Lob	dysphagia	6 yrs
Doberauer '99	F59	Le.Lob	nausea	5 yrs
Doberauer '99	F57	Ri.Lob	nausea	7 yrs
Doberauer '99	F54	Bi.Lob	nausea	simult
Pera 2001	F45	Le.lob	disconfort	7 yrs
Reiman 2001	F64	RiLob	hematemesis	13 yrs

(') this patient had a rectal metastasis as first sign

At autopsy, the stomachal metastases can present in three forms.

1. The metastases is only visible at microscopy;
2. Single or multiple intramural nodules, with or without ulceration. These are clearly hematogenous metastases.
3. Localized or diffuse intramural mass lesion that can become very voluminous, with infiltration of all layers of the wall.

Four different types have been described by Wuketich: the solely microscopic, the lenticular with small nodules, the macronodular with ulceration and the diffuse wall infiltration form.
The fourth type is certainly described. It is characterized by diffuse invasion of the whole wall and whole stomach, eventually associated with peritoneal spread, the linitis plastica (Rodde et al.).
Linitis plastica refers to the diffusely infiltrating carcinoma in a hollow organ, mainly of the digestive tract,

resulting in a rigid and somewhat thickened wall with preservation of the shape and lumen. At histology, there will be diffuse infiltration of the submucosa and muscularis, but multiple nodular metastases can complicate the picture. At radiology, it is undistinguishable from the primary stomachal linitis plastica.
Reviewing the files of the Mayo Clinics between 1950 and 1980, Couvier et al. found 31 cases originating from a breast cancer, all of the lobular cell type. In three patients, the gastric problem predated the diagnosis of the breast cancer. The interval was shorter than 5 years in 75% of the patients, but four had an interval longer than 10 years. A patient with an interval of 11 yrs was reported by Ferri et al.

As described by Caskey et al., almost all cases with stomachal metastases had retrocrural (below diaphragm), celiac, paraaortic or peripancreatic metastatic lymph nodes. More CT data are necessary to obtain an insight on the pathway how breast cancer reaches the stomach. Most probable is lymphatic reflux from a 'filled' mediastinum is the main mechanism.

Table 8. 123 - Cancer of the Breast
Metastases to the Stomach (N=51)
Data of the series of Taal et al.

Features		Symptoms	
Side of Primary		Nausea/vomiting	41%
Right 34, Left 17 (p<0.01)		Pain, pyrosis	53
Pathology		Anorexia	70
Ductal carcinoma	10	Dysphagia	20
Lobular carcinoma	36	Melena, Hematemesis	12
Undifferentiated	5	Perforation	(1)

Table 8.124 - Cancer of the Breast
Metastases to the Stomach (N=27)
Endoscopic features at diagnosis (Taal et al.)

	Histology		
Feature	Ductal (N=10)	Lobular (N=36)	Undiffer. (N=5)
Biopsy positive	9	23	3
`Repeated positive	1	5	0
Negative	0	8	2
Loca. Large ulcer	3	5	0
Polypoid aspect	1	0	0
Diffuse			
Linitis	3	14(38%)	4
Erosions	1	2	1
Gastritis	1	3	0
Extern.Compression			
Cardiac Stenosis	1	5	0
Pyloric Stenosis	0	7	0
Localization			
Proximal	1	5	0
Middle	4	6	1
Distal	0	11	0
Diffuse	5	14	4

The extension of the stomachal metastases can be large, with involvement of neighbouring structures such as the colon and the duodenum. Two patients of the series of Caskey et al. had invasion towards and through the diaphragm. Perforation is rare. Only one case was reported (Abboud et al.). In most patients reported other metastases were also observed.

From a large series of 15,983 BC-patients, Taal et al. retrieved 59 (less than 0.5%) patients who were found to have stomachal metastases. The important features are outlined in tables 8.123 & 124.
Most of the cases will have the lobular (infiltrative) carcinoma histology, although overall they are less than 20% in the primaries. This can also be seen in table 8.123, where 18 of the 29 reported cases were of the lobular type. In several reports, however, the histology was not adequately reported.
Reporting on six cases, Schwarz et al. have stressed the difficulties that can be encountered at pathology to distinguish between a secondary and a primary gastric cancer. Note that Taal et al. found 4 stomachal primaries at endoscopy in patients with BC.
Diagnosis of stomachal metastases is presently made with endoscopy and biopsy. Echography at endoscopy will allow a detailed study of the gastric wall but its findings are aspecific and have a low impact on further diagnosis.

Metastases to the Duodenum

This is a rare metastatic site, or at least not frequently reported (table 8.125). The diagnosis is made either by endoscopy, or radiology, or even CT. As histology is not always reported in the literature, the histology factor cannot be evaluated.

Table 8. 125 - Cancer of the Breast
Metastases to the Duodenum
Cases reported in the literature

Author	Pat	Primary	Symptom	Interval
Asch 1968	F57	??	Nausea -vom.	3 yrs
Azzarelli '82	F49	??.Lob	Jaundice	4 yrs
Houghton '87	F74	Le.Carc	Vomiting	6 yrs
Barendregt '89	F40	Ri.Duct	Epig.pain	12 yrs
Elliott 1995	F61	??	Vomiting	4 yrs

Metastases to the Small Bowel

A solitary nodular involvement is uncommon and has only been reported on few occasions. Any site within the bowel may be involved. The involvement can be single or at multiple segments, even diffuse with or without mesenterial invasion.

A few cases have been reported that were diagnosed after obstruction (Stellakis et al.). Rare cases presenting with perforation have also been published (Cornu-Labat et al.). Histology is not always precised, but is usually lobular. The interval is as usual for intestinal breast metastases very long (table 8.126).
At autopsy, a larger number of 'asymptomatic' metastases associated with peritoneal and mesenterial carcinomatosis can be uncovered.

Table 8.126 - Cancer of the Breast
Metastases to the Small Bowel
Cases reported in the literature

Author	Pat.	Histology	Symptom	Interv
Boulez 1975	F51	Le.Carc	Colics	5 yrs
Rees 1976	F66	Le.Carc.	Obstruction(')	Simult
Weisberg 1982	F69	Bil.Lob	Chron.diarrhea	12 yrs
LeBouedec '93	F61	??.Lob	Pelvic mass	5 yrs
LeBouedec '93	F57	??.Lob	Obstruction	6 yrs
LeBouedec '93	F55	??.Lob	Pelvic mass	3 yrs
LeBouedec '93	F59	??.Lob	Obstruction	2 yrs
Cornu-Labat'98	F39	??I.D.	Acute abd.pain	7 yrs
Stellakis 1999	F77	??.Carc	Obstruction	??

(') neglected case, tumor present for 16yrs

Metastases to the Appendix

These are rare and apparently more an incidental finding at surgery for a local syndrome (table 8.127). It is likely that presently ultrasonography can detect a tumoral process.

Table 8.127 - Cancer of the Breast
Metastases to the Appendix
Cases reported in literature

Author	Pat	Primary	Complaint	Interval
Latchis 1966	F45	Le.Duct	Acute pain	6 yrs
Maddox 1990	F65	Ri.Duct	Colics	5 yrs
Ostrowski 1996	F83	??.Carc	Pain RFI	5 yrs
Phillipart 2000	F37	Cancer	Ac.Pain RFI	3 mo

Metastases to the Colon

From a consecutive series of 3,500 patients with breast cancer, 17 patients were found to have a colorectal metastasis, confirmed at endoscopy and biopsy, excluding however those with obvious ascites. The histology of the few reported cases was in almost all the lobular type (Rabau et al.). The data of Taal et al. confirm it. The characteristics of the reported patients are in table 8.127.

Linitis pathology has also been observed, as described for gastric metastases, but much less frequent. Nevertheless, Fayemi et al. could retrieve reported 20 cases already in 1979.
Lobular carcinoma is always the histology, and the few cases reported had a long interval after first treatment, up to ten years (Gifaldi et al.). The infiltration of the wall may be complicated by masses obstructing the lumen visible at radiology as apple-core lesions, with preservation of the mucosal lining.
Relatively frequent in primary colonic cancer because of the mucosal origin is presentation with ferriprive anemia. This is uncommon in metastatic cancer as it involves the submucosa. Koutsomanis et al. have reported on a woman presenting with 1.6g/L hemoglobin, where eventually a stenosing metastatic tumor was found at the hepatic flexure, 3 years after mastectomy.

Table 8.128 - Cancer of the Breast
Metastases to the Rectum and Colon (N=17)
Data of Taal et al.

Features		Raiology	
Side of Primary		Site	
Right 11, Left 6		Cecum	3
Axillary Positive	5	Ascendens	9
Supraclavicul.node	6	Transverse	10
Pathology		Descendens	7
Ductal carcinoma	1	Sigmoid	9
Lobular carcinoma	15	Rectum	7
Slide not available	1	Type of Lesion	
Symptoms		Multiple	8
Diarrhea	11	Solitary	5
Crampy pain	10	Diffuse	3
Vomiting	4	Total obstruction	1
Mass palpable	5	Stenosis	
Gastric and colorectal	3	Median length	19 cm
		half lumen open	14
		>more than half	3
		Extrinsic impression	8
		Irregular contour	4
		Apple core lesion	3
		Mucosal destruction	3

Another particular type of colonic involvement, is the 'chronic diarrhea' form masquerading a Crohn's disease clinically and also at radiology. The several negative biopsies at endoscopy even at surgery, because of the diffuse submucosal involvement can delay the diagnosis with months as was observed in two cases (Boulez et al.; Weisberg et al.). At pathology, the involvement can be extensive with encasement of several small bowel and colonic segments. This aspect has been extensively discussed by Madeya et al. They retrieved 13 breast cancer patients with 'Crohn-like' symptomatology from the literature. They noted that the symptomatology can occur either before the diagnosis of the primary or very late, even as much as 10 years. The metastases can involve all segments of the tract, butthere may be peritoneal and mesenterial inplants and linitis aspect seen at surgery.

Metastases to the Rectum and Anal Canal

Compared with the colon's length, metastases to the rectum are not rare, but they are probably less difficult to diagnose, in view of their symptomatology and accesibility. In the series of 17 colorectal metastases of Taal et al., 7 were in the rectum.
Some were discovered at the same time as the diagnosis of the primary, as the patient mentioned both the rectal symptomatology and the breast tumor. In one patient, the metastasis preceded the diagnosis of the primary by one year (table 8.129). Remark also the high number of lobular histologies.

Metastases to the Spleen

Relatively frequent in mammary carcinoma, splenic metastases tend to be somewhat asymptomatic unless in certain pathologic states.

At autopsy, involvement is found in around 6 to 13%. Cifuentes reported a figure of 15% in 707 patients.

Table 8. 129 - Cancer of the Breast
Metastases to the Rectum and Anal Canal
Literature Cases reported

Author	Pat	Primary	Symptom	Interval
Rees 1976	F55	Ri.Carc	Constipation	1 yr
Lasson 1982	F69	Le.Carc.	Tenesmus-Blood	11 yrs
Hoff 1983	F50	Le.Lob.	Tenesmus	1yrANTE
Hoff 1983	F55	??.Carc	Tenesmus-Blood	7 yrs
Haubrich 1985	F56	Le.Carc.	Dyschezia	3 yrs
Grosdidier '85	F63	Ri.Lob.	Tenesmus	1 yr
Grosdidier '85	F56	Ri.Lob.	Tenesmus	3 yrs
Dawson 1985	F70	Le.Lob	Discharge (')	3 yrs
Clavien 1990	F82	??.Lob	Diarrhea	Simult
Darcha 1993	F60	Ri.Lob	Tenesmus	Simult
LeBouedec '93	F60	??.Lob	Tenesmus(")	Simult
Elliott 1995	F66	??.Lob	Change habit	2 yrs
Thaler 1995	F72	Le.Lob	Incontinence	6 yrs

(') metastases in the anus
(") probably same case as Darcha

In 38 successive autopsies of metastasized breast cancer, Niedobitek et al. observed splenic metastases in 14 or 37%. In 7 there were macroscopic nodules, 3 with amyloid infiltration, diffuse pulpa and follicle-carcinosis and in 4 the metastases could only be found at microscopy.
A patient (F39) presented with acute pain in the left abdomen. At CT a large mass was noted in the spleen, at surgery a multi-loculated cystic mass was found with an adenocarcinoma histology (Newmark).

It seems that invasion of the spleen can lead to patho-physiological problems such as hypersplenism (a case of Dunn et al.) or presenting as idiopathic thrombo-cytopenic purpura (Cummings et al.; Plouvier et al.).

CT is presently the imaging method of choice for t diagnosis of a splenic involvement.

Metastases to the Urologic System

Breast cancer rarely metastasizes to the kidney. Only a few cases have been reported, although at autopsy it apparently amounts to 14% (Cifuentes et al.) They observed no difference between kidneys, but bilateral involvement was noted in 64 of the 97 patients.
We are aware of only five reported cases. Hematuria occurring 3 years after mastectomy (Ridlon et la.) and flank pain 5 years (Desai et al.) were the presenting symptoms. Both cases concerned the left kidney. Histology was no more detailed than adenocarcino-ma. In both cases the kidney had been completely replaced by a tumorous mass.
Another case (F51) was reported by Takehara et al. A 'routine' follow-up CT 16 years after mastectomy dis-closed a solid mass within the right kidney. It was a solitary metastases. A percutaneous biopsy was confir-med the metastatic nature.
Within a series of 27 cases of renal metastases, Choyke et al. mention two patients with breast cancer. They observed that these metastases were multiple with poor enhancement and somewhat similar to cysts.
According to Takehara et al., two other cases should have been reported in the Japanese literature. Another concerned an adenoid cystic carcinoma of the breast (Herzberg et al.).

More frequent is ureteral involvement, an uncommon metastatic site in oncology. Breast cancer are a fre-quent primary in ureteral metastases, either intramural or more frequently extrinsic and within the periure-teric tissues. A literature review in 1986 disclosed that about 20% cases of the metastatic ureteral involve-ments were caused by breast cancer (Akmal et al.).
Reviewing the autopsy records of 181 cases with breast cancer, Geller et al. observed ureteral metastases in 15 patients or 8.3%. In half of them they weres bilateral. The major pathology is hydroureter or/and hydronephrosis, as the obstruction can occur at every level. The involvement is usually described as stricture, narrowing or encasement and is probably more frequently extrinsic by a tumorous mass along the ureter (Chu et al.). Less frequent is involvement of the ureteric wall. As mentioned by Geller, other author also stress bilaterality, compared with other primaries (Giuliano et al.).

Symptomatology is very variable. In the series of six patients reported by Recloux et al. Pain, recurrent infections, oliguria and anuria were observed. The delay between first surgery and the diagnosis of ureteral metastases varied from 2 to 14 years. Most patients had several other metastase, principally in the abdomen, indicating encasing of the ureters by carci-nomatous plaques.
One patient (F48) was reported as presenting with pain in the left flank to the thigh, hematuria and fever six years after a mastectomy. Investigations led to the diagnosis of hydronephrosis and rupture of the renal pelvis due to a metastatic mass invading the ureter and pelvis (Luciani et al.). In the more recent literature, cases with lobular histology have been reported (Lopez-Martinez et al.). Perez-Mesa et al. could report on 11 patients from a series of 341 or 3.3%.

Every oncologist is aware that radionuclide bone survey can detect abnormalities in the ureteral flow such as impairment or absence. In breast cancer this can point to a pelvic or peri-ureteric problem. This can be associated with a retroperitoneal mass as metastatic lymph nodes, not uncommon in breast cancer (Feun et al.). This particular presentation was examined in more detail by Wilkinson et al. Patients who had undergone regular bone scanning and showing pro-gressive ureteral retention, were found to have a diffuse infiltration of the retroperitoneum, often encasing the ureter and associated with hydronephrosis, but not hydroureter. They observed that it occurred exclu-sively in patients with lobular carcinomas.

Metastases in the urinary bladder are also infrequent, though several cases have been reported (table 8.129). Reviewing the literature in 1970, Pontes et al. could retrieve 22 cases from breast cancer.
Half of the patients, a sshowed by the table, is older than 65years and the long interval between diagnosis of primary and of the bladder metastases is striking. Several patients had, according to the reports, many other previously diagnosed or concomittant metastases.

Table 8.129 - Breast Cancer
Metastases to the Urinary Bladder
Cases reported in the literature

Author	Pat	Prim	Site of M	Interval
Pontes 1970	F67	Ri.Carc	Right half	8 mo
Pontes 1970	F57	Ri.Anapl.	Right wall	4 yrs
Haid 1980	F45	??.Carc	two sessile	5 yrs
Haid 1980	F83	??.Carc	mult.nodules	3 yrs
Haid 1980	F76	Ri.Carc	no endoscopy	2 yrs
Haid 1980	F71	??.Carc	Left wall	3 yrs
Mairy 1982	F40	Ri.Carc	Wall (')	9 mo
Mairy 1982	F57	Ri.Carc	Le.wall	Simult
Silverstein'87	F66	Le.Duct	Right wall	14 yrs
Silverstein'87	F54	Bil.Duct	Right wall	6 mo
Williams '92	F79	Bil.Carc	Vault	6/30 yrs
Berger 1992	F78	??.Duct	Right wall	no data
Berger 1992	F70	??.Carc	'tumor'	7 yrs
Berger 1992	F65	Ri.Lob	no endoscopy	3 yrs
Lucas 1996	F64	??.Carc	'tumor'	1 yr

(') incidental finding at oophorectomy

The revealing symptomatology is either hematuria or hydro-ureter with or without flank pain. Bladder problems such as frequent micturition, nycturia and pain post-miction, are frequently cited in the reports.
Cystoscopic findings were usually one infiltrating and ulcerated tumoral mass, but in some multiple nodules were observed. One patient with a pedun-culated metastatic bladder tumor was described (Perez-Mesa et al.). In a few patients, extensive pelvic and retroperitoneal infiltration was observed with encasement of the ureters the bladder wall and the also pelvic tissue.

Metastases to the Ovaries

The gynecological organs most frequently involved are the ovaries.
The problem of ovarian metastases from breast cancer has been adressed in the literature in several ways.
Before 1950 there were only case reports of clinical or autoptic confirmed cases.

The detection of ovarian metastases depends on clinical examination or screening echography when a certain dimension is reached (sensibility), but they cannot be distinguished from other ovarian malignant pathology (specificity) (Oram et al.). The prospective ultrasonography of the abdomen has no sense in the follow-up of breast cancer patients.
It is well known that patients with breast cancer can develop gynecological tumors later on. The most frequent are endometrial and ovarian carcinomas (Doherty et al.).
The method of detecting measurable disease varies according to anatomical site. Some can be found on clinical grounds alone, but most by imaging methods. Subclinical disease is demonstrated by histology study. For ovarian metastases, detection depends on clinical examination or screening echography when a certain dimension is reached (sensibility) but cannot be distinguished from other ovarian malignant pathology (specificity). Prospective ultrasonography of the abdomen has, however, no sense in the follow-up of breast cancer patients.

Metastases in the ovaries from a breast cancer are not an unusual location. Carcinoma of the breast is reported as the origin of ovarian metastases in about 40% of the cases, about as much as from tumours of the colon.

Ovarian metastases from breast cancer occur by hematogenous spread. Only in case of diffuse abdominal or peritoneal involvement, contigual spread can be invoked. Metastases in the ovary can be either asymptomatic as it mostly is, or symptomatic. Carcinoma of the breast is reported as the origin of ovarian metastases in about 40% of the cases, about as much as from tumors of the colon.

Two reports in the literature have concerned the rare clinical situation where ovarian metastases appeared first and before the diagnosis of the primary breast cancer was made. These are an oncologic curiosity alike cancer of an unknown primary. They should remind the gynecologist, that an ovarian mass may occur in patients even without any oncological past. In this setting, breast cancers acounted for 20% (Ulbright et al.) of all primaries detected. Prior to 1950, there had been only case reports with clinical diagnosis or confirmed at autopsy.

Some literature series are flawed by the fact that many pelvic and/or abdominal cancer patients are included whose ovarian metastases have already been found at the first (staging) operative procedure. Tumors of the colon and of the gynecological sphere can show ovarian metastases at that stage. In breast cancer however, staging laparotomy is never done, so that one has to rely on the complaints of the patient or on the fortuitous discovery of an ovarian mass when pelvic examination is performed because of pelvi-abdominal complaints or as part of a systematic follow-up.
The published series mainly concern patients diagnosed before the ultra-sonography era, and the method of detection of the tumor is never stated, nor is the incidence in the cohorts followed.

The interval after which ovarian metastases are found will vary with the follow-up length. Webb et al. stated that in their 109 breast cancer patients with ovarian metastases, 94% were found within 10 years of follow-up. Demopoulos et al. state an average interval of 61.6

months (about 5 years), but give no range, while Yazigi et al. report an interval of 15 months up to 17 years, for all their 29 patients with ovarian metastases, of which only 5 were breast cancer patients.
Gagnon et al. collected 59 cases with ovarian metastases from breast carcinoma, of which 32 diagnosed at surgery, probably for prophylactic or 'curative' ovariectomy and only 5 because of a pelvic mass. At autopsy ovarian metastases were found in another 22 patients. In 31%, it concerned only micro-metastases and only in 9 cases the metastatic tumor was larger than 5 cm. As reported in other series, more than 60% were bilateral.
The overall median interval between diagnosis of the primary breast tumors and diagnosis of the ovarian metastases is 12 months, with individual cases in this series up to 69 months. The interval of those treated for a pelvic mass was not reported separately.
We have reported a patient in whom the diagnosis of solitary ovarian metastases was made 11 years (132 months) after treatment of the primary tumor, on the basis of clinical symptoms.

In the actual setting, where more patients are diagnosed and treated at earlier stage than decades ago, ovarian (and other) metastases may well occur later or even less frequently, due to the various different adjuvant therapies, but this is difficult if not impossible to prove. In autopsy series between 12 and 23% of the breast cancer patients have ovarian metastases. Most studies have not differentiated them according to histological type, nor reported the age distribution. Literature data are in table 8.130.

Data concerning the dimensions of the metastatic tumor mass are scanty. Gagnon et al. found 31% smaller than 1 mm, 17% between 1 and 10 mm, or 48% smaller than one centimeter. Clinical examination can hardly detect such small tumors within the pelvis. The same authors show, nevertheless, that 15% are larger than 5 cm. Demopoulos et al. report an ave-rage size of 4.4cm in 32 breast cancer patients. Litschgi et al. found microscopic involvement in 16 (43%). The recent series of Fujiwara et al. detected microscopic metastases in only 25% of the 60 breast cancer cases. Several authors have unsuccesfully tried to find a relationship between histological type and the location of metastases.
Several factors are probably implicated in the anatomical location and frequency of the ovarian metastases. The influence of age with its influence on the biochemical, the hormonal and immunological state of the patient, is as poorly understood as other factors. Age must undoubtedly have an influence on the rumor biology, its aggressiveness and probably on metastatic location. The biological behaviour of breast cancer is probably also age- dependent. How this interferes with the implantation of the metastases and their further evolution can only be only speculative. Several authors have pointed out that the metastases are less frequent with increasing age (Basserman et al.). delaMonte et al. showed a declining trend with age for metastases in the endocrine organs.

According to the literature (table 8.131), patients with ovarian metastases are on the average younger than the whole group of breast cancer patients with metastases.

Table 8.130 - Breast Cancer : Ovarian Metastasis : Data from literature reports

Author Year	N (breast)	N (all)	% breast	Bilateral	Interval	Age
A. As First presentation (type 1)						
Young 1981	2+3	--	--	N.G.	< 0(')	N.G.
Ulbright 1984	7	35	20%	3/7	< 0(')	N.G.
Favre 1986	1				< 0(')	48
B. Therapeutic Oophorectomy (type 3A)						
Israel 1965	13	33	39	72% (all)	N.G.	N.G.
Green 1965	27	64	42	N.G.	up to 11yr.	21 premenop
Lee 1971	18 (24% of BC)	--	--	N.G.	N.G.	N.G.
Litschig 1975	16 (34% of BC)	--	--	13/16	N.G.	m 46.5 yr
Horvath 1977	12 (28% of BC)	--	--	N.G.	N.G.	N.G.
C. Clinical Follow-up (type 3B)						
Webb 1975	109	357	30.5%	N.G.	94% within 10 yr.	N.G.
Demopoulos 1987	32	96	33%	19/32	mean 61 mo	15 premenop.
Yazigi 1989	5	29	17%	N.G.	15m-17yr (m 27mo)	N.G.
Petru 1992	28	82	34%	71%	N.G.	med.52(21-74yrs)
Ayhan 1995	27	168	16%	48%	N.G.	N.G.
D. Autopsy (type 4)						
Fujiwara 1995	13	60	21.6%	78% (all)	N.G. no ov.met.	at death 48.5 yr 59.3yr.
E.Mixed Serie						
Gagnon 1989	59	--	--	32/59 (54%)	mean 11.5 mo.	25-80 yr average 48.6 yr.

(N.G. not given; m: mean; BC: Breast Cancer)
(') diagnosis of metastases before of the primary.

In the series of Green et al., 21 of 27 are premenopausal, but only 15 of the 32 in the series of Demopoulos et al. The mean age of the patients averages between 46.5 years (Litschgi et al.) and 48.6 yrs (Gagnon et al.). The clearest demonstration is in the autopsy serie of Fujiwara et al., where breast cancer patients with ovarian metastases were about 10 years younger than those without these metastases (48.5 years vs. 59.3 years).
In an extensive study of 168 operative patients with type 3 ovarian metastases, Ayhan et al. had 27 or 16% with breast cancer patients. They provided some interesting details: 40% had ascites, 48% were bilateral at gross inspection, but 63% when microscopic studies was performed.
Another study by Petru et al. found 28 or 34% breast cancer in a series of 82 operative (type 3) patients. Remarkable is that 8 of the 28 or 28% were lobular carcinomas.
Bilaterality was present in 71% and 68% had abdominal disease. They mention that of the 31 with known primary 20 were breast cancer. Of the 31 patients in whom the primary was not known, details were not shown.

Gersell et al. have stressed that correct diagnosis is important, especially when the primary is unknown, because it can result in delayed identification of the primary and inappropriate or insufficient treatment.
In the era of prophylactic oophorectomy as an adjuvant setting in young patients, quite a large number of microscopic as well as macroscopic metastases were found in the ovaries.
In this group of patients, known to have metastases on clinical ground, it was evident that they also could have metastatic a substantial number deposits in the ovary. This ranged from 24 to 42%, depending on the diligence of the pathologist. In the report of Horvath, 28% of the 42 patients had ovarian metastases, being micrometastases and bilateral.

The concerned patients already with known metastases, are different from the whole group of patients being followed after treatment. The majority of them will probably go unnoticed in the follow-up.
A few authors remarked that ovarian metastases are proportionally more frequent in patients with lobular carcinomas (LC). Ulbright et al. found in their 7 breast cancers revealed by ovarian metastases, 4 of the lobular type.

Harris et al. reported a substantial difference in metastases in endocrine organs, as lobular had more (not significantly) adrenal metastases, but significantly more, about 14 times, ovarian metastases than ductal carcinomas.
They were the first to demonstrate the propensity of LC to metastasize more frequently to some unusual sites as the peritoneum, the retroperitoneum, hollow viscera and the leptomeninges.
Comparing their autopsy reports in 25 LC and 195 DC, Lamovec et al. found no significant difference for adrenal (44%-23,2%) and thyroidal metastases (12%-7.2%), but a highly significant difference in ovarian metastases (52%-11.32%) at a $p<10^{-6}$. No other endocrine organs were studied.

More recently, Bumpers et al. compared at autopsy more specifically the metastatic pattern in endocrine organs for lobular carcinoma in 32 subjects. The relative frequency of endocrine organ involvement is greater for lobular carcinoma, but the global pattern is indeed the same. There is a significantly higher incidence of ovarian metastases, but also for the pituitary and the less frequently studied parathyroid glands (table 8.115).

Metastases to the Uterus

Breast cancer metastatic to the uterus is not unusual. It mainly involves the endometrium and less frequently the uterine cervix. In most of the case reports the presence of multiple other metastatic sites are mentioned, but the metrorrhagia is dramatic enough to be investigated. The rarity of this presentation means that diagnosis of a metastatic disease is not immediate, unless several other metastases are already present or previously treated.
Except for the case reports (table 8.132), a series of 17 cases from one institute has been reported by DiBonito et al., based on autopsy reports. In five patients, the cervix was involved, but many with myometrial involvement.

Table 8.132 - Breast Cancer
Metastases to the Endometrium reported

Author	Pat	Primary	Extension	Interv.
Rivel 1984	F51	Bil.Carc	+Myometrium	Simult
Piura 1985	F49	Ri.Carc	+Peritoneum	8 yrs
Giltrap 1986	F79	Ri.Lob	Extens.pelvic	6 yrs
BenBaruch '90	F51	Le.Lob	widespread	9 mo
BenBaruch '90	F61	Le.Duct	bone metast.	4.5 yrs
BenBaruch '90	F60	Ri.Lob	many other M	6 yrs
Gerber 1991	F54	Le.Duct	only endometr(')	1 1yrs
Fiorella '93	F54	Bil.Carc	no data(")	Simult
Taxy 1994	F68	Le.Carc	no surgery	Simult
Taxy 1994	F77	Le.Carc	no surgery	2 yrs
Taxy 1994	F34	Ri.Carc	no surgery	5 yrs
Rodier 1994	F56	Ri.Lob	no surgery	15 yrs
Mallow 1997	F42	Ri.Lob	extended, periton.	3 yrs
Lallas 1997	F63	Le.Carc	all layers	3 yrs
Kennebeck '98	F71	Le.Duct	vaginal ext.	2.5 yrs
Palazzo 1999	F65	??.Duct	no data	6 yrs
Palazzo 1999	F51	Ri.Duct	extensive	13 yrs
Martinez 1999	F78	Le.Lob	all layers	2 yrs
Martinez 1999	F58	Ri.Duct	all layers	3 yrs
Dessole 1999	F57	Le.Lob	whole uterus	2 yrs
Piura 1999	F58	Le.Duct	whole +vagina	7 yrs
Sinkre 2000	F58	??Duct	mult.+ovary	4 yrs

(') *two years later extensive cervical involvement*
(") bilateral neglected tumors

In six, only the myometrium was involved; in the other 6 the myometrium and endometrium. The single

case reportsshow that the various different layers of the uterus were concerned, and like the patients of DiBonito et al., there were widespread metastases in the pelvis, the abdominal cavity and elsewhere.
Metastases to the cervix are less common. Several reasons have been put forward to explain their lesser frequency compared to those in the endometrium (see Chapter 4). Breast adenocarcinoma metastases must be differentiated from primary adenocarcinoma of the (endo-)cervix. Immunohistochemical methods will be very helpful to certify the diagnosis. A lobular histology is somewhat easier to recognize. The main symptomatology is vaginal bleeding. A number of cases have been first presentation of an unknown breast cancer (table 8.133).
Reviewing the literature in 1988, Yazigi et al. could retrieve 21 other cases, of which 2 had metrorrhagias as first sign of a breast cancer.

Table 8.133 - Breast Cancer
Metastases to the Uterine Cervix

Author	Pat.	Primary	Pathology	Interval
Song 1963	F45	Ri.Carc	Biopsy	Simult
Song 1963	F49	Bil.Carc	Biospy	Simult
Song 1963	F51	Le.Carc	Biopsy	4 yrs
Cohan 1984	F74	Ri.Duct	Endocerv.Tu	1 yr
Tziotziotis'88	F65	Le.Lob	Tum.invasion	3 yrs
Yazigi 1988	F49	Le.Duct	Biopsy only	3 yrs
Yazigi 1988	F46	Le.Duct	Biopsy only	3yrs
Yazigi 1988	F38	Le.Carc.	Biopsy only	simult
Campora 1991	F57	Bil.Lob	Endocervical	5 yrs
Taxy 1994	F65	Ri.Carc	Conization	3 yrs
Rodier 1994	F54	Le.Duct	Bulky-no surg	4 yrs

It should be remembered that a second uterine, either endometrial or cervical tumor can occur as a second independent malignancy in patients with breast cancer. Tamoxifen has an oestrogenic action on the uterine mucosa, causing some hyperplasias of the mucosa leading to metrorrhagia (Jordan et al.). This drug also enhances the risk of development of an endometrial carcinoma (Fischer et al.). In our patient reported, it was most probably responsible for the glandulo-cystic hyperplasia of the endometrium and the leiomyomata, observed at surgery for the bilateral ovarian metastases.

Metastases to the Vulva and Vagina

Although a rare site for metastasis, breast cancer is also the most frequent primary to metastasize in the vulva. A point to remember is the possibility of an ectopic, vulvar breast cancer, but this is rare. The presence of a primary breast cancer is an argument in favor of metastatic disease, either solitary or associated with other metastasis. Only a few cases have been reported (table 8.134). It is not impossible that metastases occur more frequently, although a gynecological examination is rarely performed in cases of metastatic disease.

Table 8. 134 - Breast Cancer
Metastases to the Vulva reported

Author	Pat	Primary	Site of M	Interv
Dehner 1973	F			
Mader 1982	F61	Ri.Carc	Ri.labium maius	Simult
Beuzeboc 1995	F74	Ri.Lob.	Labium Maius	15y rs
Patsner 1996	F48	Bil.Duct	Le.low.vulva(')	1 yr
Curtin 1997	F61	Ri.Duct	Labium maius	6 yrs
Sindico 1998	F79	Le.Duct	Le.Labium minus	12 yrs
Menzin 1998	F53	Le.Lob	Le Labium maius	Simult

(') described as a metastasis in Bartholin's gland

Breast cancer metastatic to the vagina is very rare. We are aware of only one report. In autopsy series, this is almost never reported. No details were given in the few cases that have been reported.

A woman presented with bilateral breast tumors and abdominopelvic malaise. Gynecological examination disclosed an infiltrative tumor in the vaginal wal. Histology disclosed the same carcinoma at both sites (Pineda et al.). In the case reported by Piura et al. there was extensive contiguous involvement of the cervix and of the vaginal wall.

Causes of Death

The chief cause of death in mammary carcinoma is the interference by the cancer metastases on organ function, or secondary to the neighbouring involvement. Pulmonary, liver and brain involvement are the most common. Other sites implicate more complications such as bone fractures, spinal cord compressions or causing secondary problems such as urinary infections.

Table 8. 135 - Breast Cancer
Causes of Death (N=166)
Data of Hagemeister et al.

Cause	%	Cause	%
Pulmonary Insuff.	26%	Hemorrhaging	9
Metastases	17	Thrombocytopenia	1
Restrict.Disease	8	Local tumor invas.	1
Miscellaneous	1	DIC syndrome	2
Cardiac	15	Anticoagulants	1
Myocard infarct	3	Organic disease	4
Congestive failure	4	CNS-failure	9
Organic disease	4	Meninges	4
Drug related	1	Brain	4
Pericardial inv.	4	Tumor Emboli	1
Pulmonary Embol	1	Miscellaneous	1
Tumor Embolism	2	Infections	24
Hepatic failure	14	Pneumonia	14
Hypercalcemia	2	Other	10

Some reports have included a discussion of this issue. The report by Hagemeister et al. is very detailed (table 8.135). It seems that the metastases are directly responsible only in 50% of the patients, while the other patients die of cancer- or treatment-related complications.
In a series of 144 breast cancer patients, Cho et al. observed a certain degree of progressive increase of

infection-related deaths, while the directly cancer-related deaths decreased. Hemorrhagic complications did not change proportionally over the period studied (1966-1975). We have found no further data in the literature, nor about eventual modifications through treatment.

Metastases during Follow-up

During the last decades, several studies have tried to obtain an insight into the utility of the different imaging methods for an early detection of locoregional and particularly of distant metastases. It was hoped that regular appointments and extensive examinations would permit earlier and more effective treatment. Several studies have already concluded that regular systematic examinations do not influence the survival rate. In this era of cost-containment, it then becomes difficult to enforce regular examination, and more to perform them only if the patient becomes symptomatic. A standard time-program of any regular examination schedule has never been implemented. This should be difficult, since no one has an insight in the time-lapse of the various different metastases if any appears (see Kocsielny et al.). Moreover, the yield is low as the occurrence of metastases is apparently spread out over a long time.

Some data have been reported by Wagman et al. They observed in 208 patients, that most recurrences occurred within 3 years (fig.8.28). They noted some differences on the mean interval for different metastatic sites (table 8.136). There is apparently only some gain in the detection of pulmonary and bone metastases by scheduled examinations.

Table 8. 136 - Breast Cancer
Mean Interval for different Metastatic Sites
Data of Wagman et al.

Site	Time to discovery (months) At symptom	Scheduled
Contralateral	10.0	36.1
Locoregional	49.0	25.9
Bone	33.0	23.8
Lung	49.3	25.9
Liver	53.0	53.0
Multiple	25.6	---
Any	31.8	31.4

Wagman et al. (fig.8.28) and Neises et al. have both reported interesting data. There is a progressive increase in the metastatic rate in the first year, both in the symptomatic and the scheduled group. The most efficient detection method seems to be clinical examination and the anamnesis, as they were able to detect nearly half of the distant metastases in the series reported by Neises et al. (fig.8.29 & 30). Since local recurrences account for the majority, they may indeed be detected on that basis.

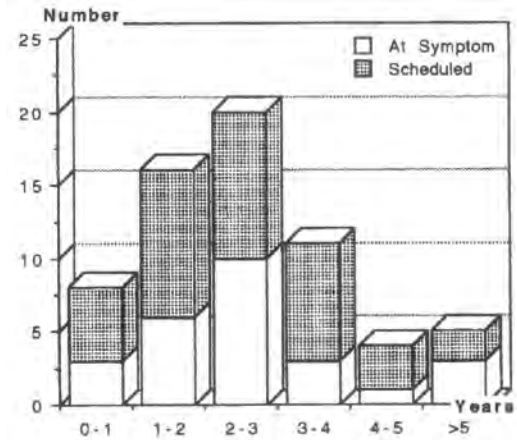

Fig.8.28 - The respective incidence of distant metastases in the follow-up of 208 patients with breast cancer (Drawn from data of Wagman et al.)

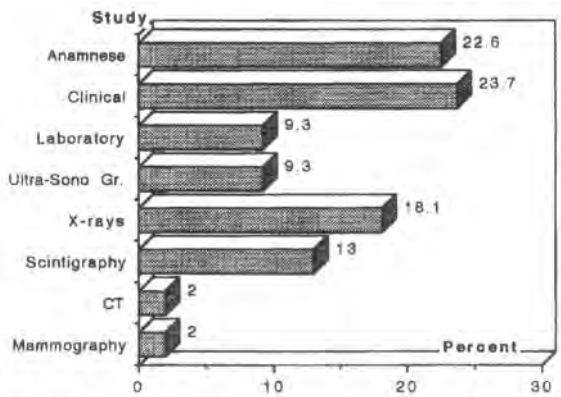

Fig.8.29 - Efficiency of the different examinations performed at ambulatory follow-up in 1,189 patients with breast cancer. (Drawn from data of Neises et al.)

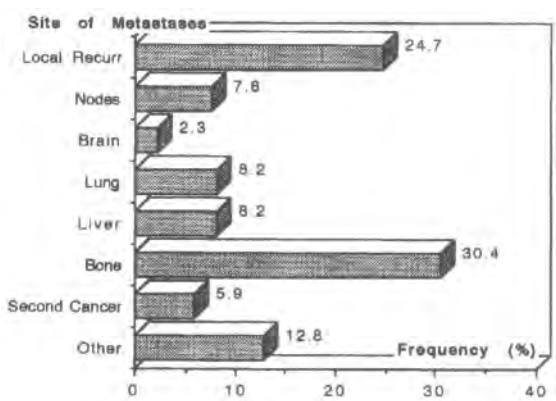

Fig.8.30 - Site of first-event during follow-up observed in 1,189 patients with breast cancer (Drawn from data of Neises et al.)

Table 8. 137 - Breast Cancer
Positivity of Imaging during Follow-Up
Data of Wieland et al.

Time (mo.)	Chest X-rays N=385(')	US.Liver N=404	Mammo N=397
0.-3	1.6%	1.2%	3.0
4-12	1.2	1.0	1.0
13-24	4.7	1.4	2.1
25-60	4.7	4.3	3.9
>60	2.0	1.4	5.6
Stage			
T1	5.0	6.4	11.4
T2	10.0	6.5	9.5
T3	13.6	6.8	6.8
T4	20.0	6.7	6.7

(') N at diagnosis of primary

The efficiency of the different routine examinations performed in the follow-up of breast cancer seems indeed very low. Detailed data have been reported by Wieland et al. (table 8.137).
Their data prompt the conclusion that a yearly chest X-ray and a good clinical examination should suffice, unless some alarming or other symptoms occur.
As already mentioned, there is clearly a higher incidence of events in the first years. The data reported by Ciatto et al. confirm this in respect of local recurrences (table 8.138) and of Cocconi et al. in respect of distant metastases (table 8.139).
The data of Cocconi et al. also illustrate the highest incidence of events within the first three years being higher for the node-positive patients, indicating the correlation with the aggressiveness of breast cancer.

Overall Lesson

Breast cancer is known for its high incidence of regional and distant metastases. While some organs are more frequently involved, every other site can be involved, either as sole site or in association with widespread disease. It is important to remember that it can occur many years after diagnosis or first treatment.

Table 8. 138 - Breast Cancer
Incidence of Local Recurrence in first 5 years (N=1139)
Data of Ciatto et al.

Period (years)	Incidence in Node Negative	Node-Positive
0-1	1.7%	5.2%
1-2	2.2	7.9
2-3	0.9	1.9
3-4	2.1	1.0
4-5	0.6	0.9

Table 8.139 - Breast Cancer
Failure according to Interval (N=1016)
Data of Cocconi et al.

Interval	Node neg		N+1-3		N+>3	
years	Tot	Av.	Tot.	Av.	Tot.	Av.
0-3	15%	5.0	39	13	65	21.7
4-5	5%	2.5	14	7	10	5.0
6-10	7%	1.4	12	2.4	10	2.0

Every oncologist with some experience will recognize that there are a number of frequent patterns that frequently occur, and many of the breast cancer patients will fall into one of these categories, at least in the first phase of the dissemination as local only, bone only or visceral only and others. Years ago, Jessiman et al. recognized and pointed this out. The six patterns depicted on fig.8.31 are not the only ones however. They illustrate the multiple presentation possibilities of metastatic breast cancer. However, the relative incidence of the different patterns is unknown.

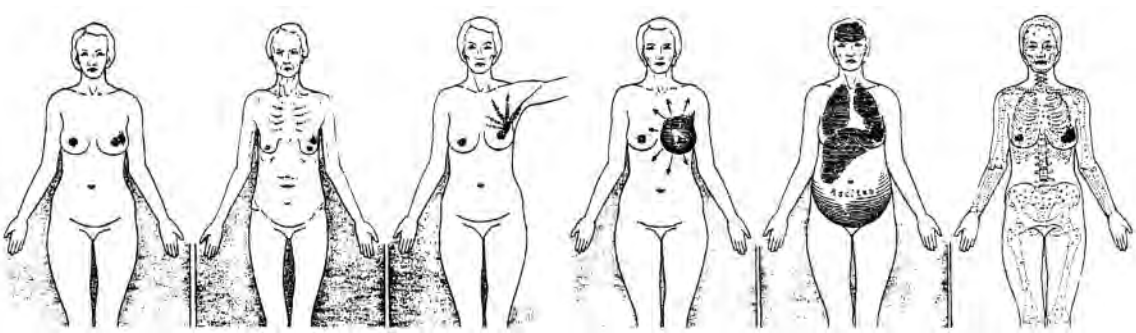

Fig.8.31 - Common dissemination patterns observed in breeast cancer: from left to right: the young and early, the old and early, slow locoregional, local fulminating, visceral only, bone only (from Jessiman et al.)

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Caution: References are given for documentary purposes. Not all have been reviewed or used in the redaction of the text. We do not claim completeness of data. The references are as much as possible grouped per subject heading. For some headings, only reports after 1979 are listed.

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9
METASTASES from TUMORS of the DIGESTIVE TRACT

METASTASES from Cancer of the ESOPHAGUS

Metastatic Pattern

The pattern of hematogenous metastases has been studied exclusively at the hand of autopsy series. However the series are not alike. They include untreated, operated and/or irradiated patients. The pattern of metastases in such patients is possibly influenced by the treatment, but data are scarce and difficult to analyze. Another major problem is the absence of a standardized autopsy protocol, and the subsequent histological examination. Metastases can be macroscopic or only microscopically confirmed.

Lying loosely within the mediastinum, esophagal tumors can easily spread into the mediastinal nodes, the neighbouring organs and structures and will have readily access to the veins causing hematogenous metastases.

A few autopsy series highlight a significant locoregional invasion into the lymph nodes and the neighbouring organs. The degree of intensity would seem to correlate with the histological type. In fact, distant metastases of esophageal carcinoma are much less frequent than in other cancers. Remarkable is that bone and brain meta-stases are even rare (Table 9.1).

Table 9.1- Cancer of the Esophagus
Modalities of spread of the tumor

1. Local invasion and contiguous spread
2. Intramural spread (longitudinal) within esophagus and/or towards cardia and stomach
3. Spread along lymphatic vessels, locoregional or distant
4. Hematogenous (distant metastases)

Local Invasion and contiguous spread

Any mucosal tumor develops first within the mucosa and will sooner or later perforate into depth. As the esophagus has no serosa, tumor cells can rapidly spread within the loose mediastinal tissues or along the lymphatic vessels (fig.9.1).

Intramural longitudinal spread has been noted as being a typical way of spread for esophageal tumors. It has been explained in terms of extension along the submucosal lymphatics.
Tumors can be divided in two macroscopic types, those with an elevation component at the tumor margins and those without (fig.9.2).

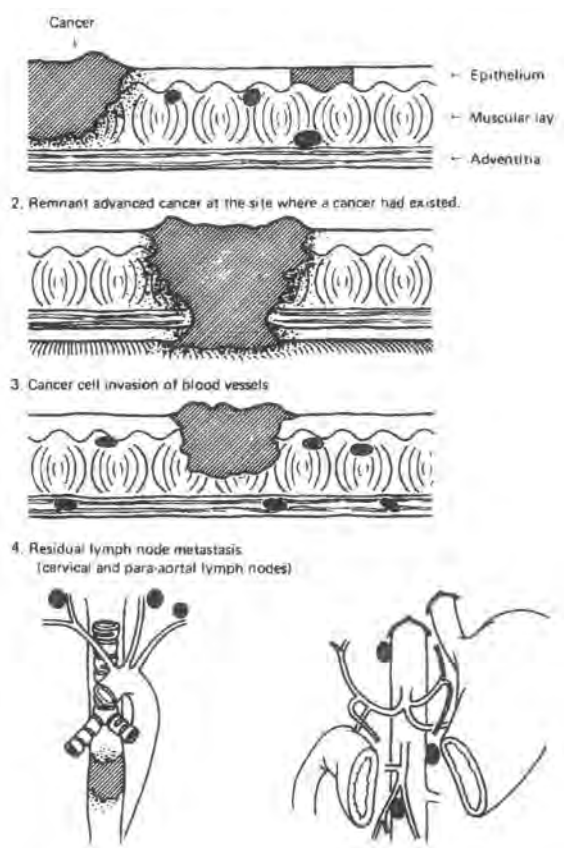


Fig.9.1 - Progression of mucosal tumor through the deeper layers and regional lymph nodes (from Isono et al., with permission)

The presence of elevation at the tumor correlates with the number of involved lymph nodes. Tumors without an elevation component have an incidence of 7% involved lymph nodes, while in case of elevation com-

ponent the amount reaches 53% (fig.9.3). The reason for this is, however, not evident.

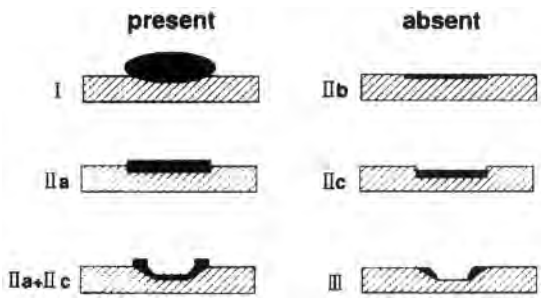


Fig.9.2- Presence or absence of elevation as macroscopic feature of carcinoma of the esophagus (Nagawa et al., with permission)

Local Contiguous Invasion

Local contiguous extension is a common feature of esophageal cancer. Due to the absence of serosa, the tumor can spread without interruption towards several thoracal and even abdominal organs. While at autopsy, 17% of the patients will have any mediastinal fistula, Chan et al. disclosed any infiltration to organs or structures adjacent to the esophagus in 45% of the 231 autopsied patients. Invasion was seen in the trachea, the lungs, the aorta, the pericardium, the heart, the diaphragm, the thoracic spine, the chest wall, the dorsal ribs and also in the stomach, the liver, the pancreas, the transverse colon and at the cervical level in the thyroid.

According to the third wherein the primary was situated, not much difference was noted in incidence of invasion. At each level, 20% of the tumors had infiltrated and perforated the mediastinum and/or the trachea. The bronchi and/or lung parenchyma were involved and perforated in about 10% (autopsy data of Sons et al.).

This mode of spread should be kept in mind, in view of the claims that resection can be done within a safe margin.

Intramural Spread

Intramural metastases present as nodular masses in the submucosa or in the muscular layer. They can be found at the oral or at the gastric side. The number is about equal at each end of the tumor, although with a tendency to be somewhat more at the gastric end. They are present in about 25% of the patients after serial sectioning (Lam et al.).

A statistical correlation has been established between the presence of intramural metastases and positive lymph nodes (Kato et al.) (Table 9.2).

As we will discuss further, quite a number of patients have metastases in the stomach. This condition is presently considered as a submucosal extension of the tumor in a mode similar to intramural metastases. In the study by Kato et al., 4.6% of the patients had intra-mural metastases in the stomach. This could well suggest that there is a free connection of the lymphatics of both organs, crossing the esophagogastric junction. An incidence of 5.6% was reported by Maeta et al. in 89 operated patients.

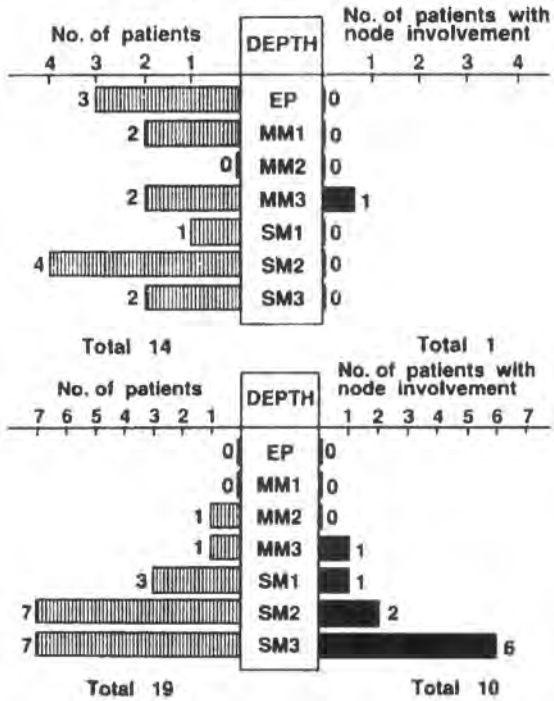


Fig.9.3 - Relation of lymph node involvement depending on the presence or absence of the elevation component (From Nagawa et al., with permission)

Table 9. 2 - Cancer of the Esophagus
Correlation IntraMural spread with Lymph Node Metastases
Data of Kato et al.

	With Intramural	Without
Tumor Size (average)	6.3±2.5	4.8±2.7
Cases with lymph node	55/60	32/60
Positive Nodes (average)	7.4±8.1	1.9±3.2

All values significant at P<0.01

Percentage of Lymph Nodes (Data of Lam et al.)
80% (N=25) 58% (N=71)

The distant metastatic rate was, however, similar in patients with or without intramural metastases (Table 9.3) (Nishimaki et al.).

Spread along Lymphatics

The regional lymphatic nodes have been 'cartographed' by the Japanese surgeons (fig.9.4).

Data of lymphatic involvement at surgery as is commonly performed nowadays are much more interesting and should guide the surgeons aiming a 'complete' dissection.

Table 9.3 - Cancer of the Esophagus Ultimately Involved Site and intramural metastases Data of Nishimaki et al. (abridged)

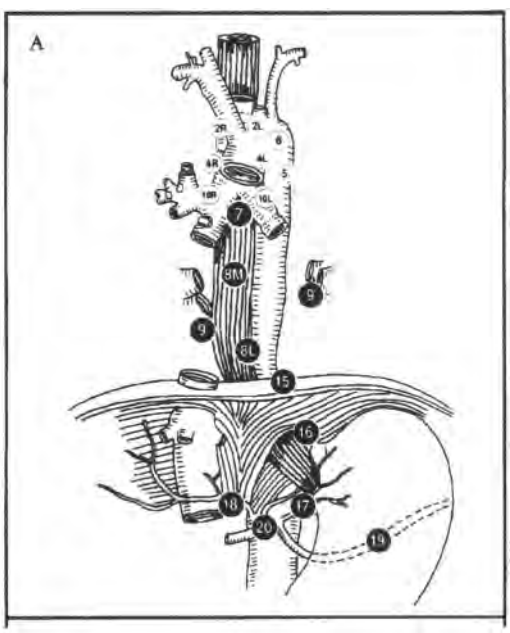
Site	With Intramural N=19	No Intramural N=20
Local	58.0%	55%
Lung	15.8	10.0
Pleura	26.3	30.0
Liver	10.5	30.0
Bone	42.1	20.0
Peritoneum	5.3	10.0
Distant Lymph Node	31.6	40.0

The lymph vessels ran predominantly longitudinally with many anastomoses between and within the four levels.

Anatomic studies by Rouvière (1938) showed collecting trunks originating from the submucosa emptying in the nearest lymph node. Some trunks in the upper two thirds also ascend in the adventitia and trunks from the lower third descend. The collecting trunks may drain superiorly as far as the cervical nodes or downwards as far as at the cardiac and even the celiac nodes.

This results in drainage in several regions. The upper third can drain to the internal jugular, cervical and supraclavicular area. The upper and the middle third drains to the peritracheal, the hilar, subcarinal and para-esophageal, periaortic and pericardial regions. The distal third can drain up to the lesser stomachal curvature, the left gastric and celiac axis.

This particularly 'extensive' lymph drainage may well explain the several unusual metastatic lymph nodes that one may encounter in clinics and surgery:



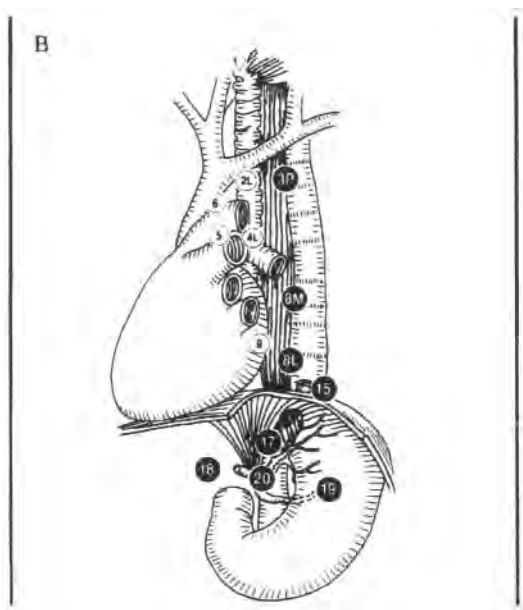


Fig.9.4 - The lymph node stations in esophageal cancer

Station	Name	Location
1	Supraclavicular Nodes	Above supraclavicular notch and clavicle
2R	Right Upper Paratracheal	Between intersection of caudal margin of innominate artery with trachea and the apex of the lung
2L	Left Upper Paratracheal	Between top of aortic arch and apex of the lung
3P	Posterior Mediastinal	Above tracheal bifurcation
4R	Right Lower Paratracheal	Between intersection of caudal margin of innominate aretry with trachea and cephalic border of azygos vein
4L	Left Lower Paratracheal	Between top of aortic arch and carina
5	Aortopulmonary	Subaortic and paraaortic nodes lateral to the ligam. arteriosum
6	Anterior Mediastinal	Anterior to ascending aorta or innominate artery
7	Subcarinal	Caudalo to the carina
8M	Middle ParaEsophageal	From tracheal bifurcation to caudal margin of inferior pulmonary vein
8L	Lower ParaEsophageal	From caudal margin of inferior pulmonary vein to esophagogastric junction
9	Pulmonary Ligament	Within inferior pulmonary ligament
10R	Right Tracheobronchial	From cephalic border of azygos vein to origin of RUL bronchus
10L	Left Tracheobronchial	Between carina and LUL bronchus
15	Diaphragmatic	On dome of diaphragm and adjacent to or behind its crura
16	Paracardial	Adjacent to the gastroesophageal junction
17	Left Gastric	Along left gastric artery
18	Common hepatic	Along the course of common hepatic artery
19	Splenic	Along splenic artery
20	Celiac	At base of celiac artery

- tumors of the upper third can metastasize to the superior gastric nodes;
- the upper third drains frequently to the cervical and paratracheal nodes;
- tumors of the lower third can drain to the superior mediastinal nodes;
- the lower thoracic and abdominal tumors will drain most frequently to the retrocardiac and celiac nodes.

Abdominal lymph node metastases are rare when the primary is in the cervical third. When the tumor is in the other thirds, cervical and abdominal lymph node metastases are much more frequent (data not shown).
According to autopsy data, nearly 70% of the patients have some form of lymph node involvement (Sons et al., table 9.4).
The most frequently involved node is the right recurrent nerve node (3P) in 33% of the middle third tumors but in 66% when the tumor is in the cervical third. More than 20% had lymphatic involvement in the mediastinal right recurrent nerve node, the left gastric nodes, the left cervical nodes, the left paratracheal, the middle peri-esophageal and right paracardiac nodes (table 9.5) (Kato et al.).

Table 9. 4 - Cancer of the Esophagus
Frequency of Lymph Nodes Involvement (N=171)
Autopsy Study of Sons et al.

Site	Involvement (%)
Any lymph node involved	67.3%
Cervical node	9.9%
Paratracheal	40.4
Peribronchial	7.6
Para Esophageal - Mediastinal	56.1
Para Gastric	23.4
Peri Pancreatic	9.4
Abdominal Paraaortic	14.0
Inguinal	0.6

Table 9. 5- Cancer of the Esophagus
Frequency of Lymph Node Involvement (N=79)
Data at Surgical Dissection (Kato et al.)

Cervical			
Ri Para Esoph.	11.4%	Mi Peri Esoph	20.3
Le Para Esoph	10.1	Lo Peri Esoph	13.9
Ri deep cervic	15.2	Infra Aortic arch	2.5
Le deep cervic	21.5	Infra Carina	17.7
Ri Supraclav	6.3	Abdominal	
Le Supraclav	6.3	Ri paracardiac	20.3
Mediastinal		Le paracardiac	17.7
Ri Recurr.Ne	34.2	Perigastric	11.4
Le paratrach	20.3	Left Gastric	21.5
Up.PeriEsoph	19.0	Common hepatic	2.5
Ri paratrach	17.7	Coeliac	8.9

Several patients have extra-thoracal metastatic lymph nodes, as the various tables show.
Cervical and/or supraclavicular lymph nodes were most frequently invaded in mid-third tumors and tumors of the lower third frequently had metastases to liver, more than from other thirds.
Presentation with cervical or supraclavicular lymph nodes first is relatively uncommon, but has been reported. Personally, we have the experience of a young women 45yrs, presenting with a mid-cervical node. Panendoscopy was negative after the histology of the node showed epidermoid nature. In view of her penchant for alcohol, radiology of the esophagus was prescribed and disclosed a large but asymptomatic tumor at the middle-third.
A neck abcess from a cluster of metastatic epidermoid lymph nodes was found to be metastatic from a thoracic esophagus tumor (Thorp et al.).

Intrathoracic Non-Nodal Spread

As the esophagus lies loosely within the mediastinum and has no serosa or other barrier, malignant tumors can penetrate rapidly into the medastinum tissue, but also the nearby contiguous trachea and bronchi. Endobronchial involvement can occur by direct extension of the tumor, but also from a metasatic adenopathy, especially when the tumor is located below the bifurcation. The invasion of these structures has been diversily appreciated and reported to be invaded in 5 to 40%, but this greatlyt depends on the stage of the patients included in the series. While 75% of the patients studied had distant metastases, Melissas et al. reported gross infiltration in 30% and early invasion in 18%.
Macroscopic abnormalities were observed in a series of 116 operable patients prospectively examined in 32% but only in 3.2% could a positive biopsy be obtained (Riedel et al.).
Interesting data have been reported by Imdahl et al. As can be expected on anatomical grounds, the frequency of endobronchial involvement was the highest when the primary was located at the proximal third (41%), while it was only 28% at the middle and 26% at the lower third; the latter leading to bronchial problems through metastatic lymph nodes.
The most pertinent data have been reported by Choi et al., in 525 patients. They observed the most frequent problems with tumors located at the upper-third (table 9.6) and with longer tumors (fig.9.5). They could also correlate the involved bronchus with the site of the tumor (table 9.6).

Table 9.6 - Cancer of the Esophagus
Abnormal Bronchoscopy (N=498)
Modified from Choi et al.

	Esophageal segment			
	Cerv.	Upp.	Mid	Lower
N	37	49	300	112
Normal	48.6%	38.8%	62.7%	87.5%
Impingement	27	36.7	17.7	7.1
Invasion	24.3	24.4	19.6	5.4

The data show that even in small cancers, bronchial involvement can occur and that tumors of the lower third also can cause bronchial problems. Mediastinal metastatic nodes are probably the cause, but this is not discussed in their report.

Table 9.7 - Cancer of the Esophagus
Site of Abnormal Bronchoscopy (N=498)
Modified from Choi et al.

	Esophageal segment			
	Cerv.	Upp.	Mid	Lower
Abnormal N	19	30	112	14
Trachea	100%	83.3%	46.3%	36.4%
Ri.Bronch.	0	0	10.2	36.4
Le. Bronch.	0	6.7	36.1	18.2
Combined	0	10	7.4	9.1

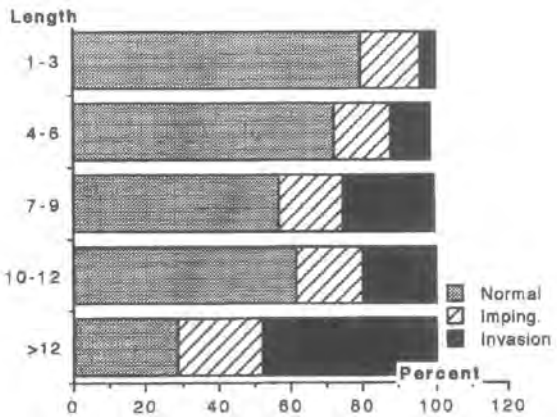


Fig.9.5 - Incidence of abnormal bronchoscopy according to the length of the esophageal cancer (drawn from data of Choi et al.)

Excluding 117 inoperable patients, 148 could be withheld where tracheobronchial invasion was not suspected. Overall invasion was confined either at bronchoscopy (23) or surgery (7), or 15% of the 'unsuspected' patients. Important factors correlating with invasion were length of the tumor, histology grading, CT findings of disappearing intervening tissue planes, respiratory symptoms and TNM-stage. Incidence of regional lymph nodes did not correlate (Riedel et al.).
A more detailed study report on site of invasion was provided by Baisi et al. on 113 patients with supracarinal esophageal cancer. A tracheo-bronchoscopy was performed in all patients. Abnormalities were observed in 116 of the 160 procedures performed or 72%. (Table 9.8)

Table 9.8 - Cancer of the Esophagus
Tracheo-bronchialInvasion (N=113)
Data of Baisi et al.

	All (')	Positive
Trachea-Carina	41 (25.6%)	41 (35%)
Left bronchus	41 (25.6%)	41 (35%)
Left Bronchus + Trachea	31 (19.3%)	31 (26%)
Right Bronchus	3 (1.8%)	3 (2.5%)
None	44 (27.5%)	116

(') percent of total number of patients (") of all positive patients

Distant Metastases

Pure hematogenous metastases are not as frequent in esophageal cancers as in others. Autopsy data however do not always separate the contiguous invasion from true distant metastases.

Table 9.9 - Cancer of the Esophagus
Status at autopsy of 93 patients (88 epidermoid)
Data of Attah et al. 1968

Lymph nodes		Distant Metastases	
Tracheobronchial	35.4%	Liver	39.8%
Peri-Esophag.	16.1	Lung	34.4
Para Tracheal	16.1	Kidney	10.7
Bronchopulmon.	9.6	Thyroid	9.6
Deep Cervical	18.2	Adrenal	9.6
Peripancreatic	13.9	Pleura	7.5
Retroperitoneal	21.5	Stomach	6.4
		Vertebrae	9.6
		Diaphragm	6.4

Data from Bosch et al. relating to 82 patients failed to show residual tumor while distant metastases was observed in 32%. They noted direct (contiguous) extension in 30 cases or 37.5%. It concerned mostly tracheo-bronchial invasion (9/30) but others had pericardial, aortic or/and pleural invasion. They reviewed 5 previously published autopsy series stressing that about the same proportions were reported.
One must further remark that a small number had metastases in the upper abdominal organs as stomach, pancreas and gallbladder aside of the liver. It is not clear if these were really metastatic cases or progressive retrograde lymphatic invasion (table 9.9).
There are apparently proportionally more metastases in the male patients than in females, but the difference is not significant (Chan et al.).

The influence of histology type was examined by Mandard et al. In patients with undifferentiated carcinoma, there were significantly more lymphatic and distant metastases (Table 9.10).

Table 9.10 - Cancer of the Esophagus
Status at autopsy according to histology
Data of Mandard et al.

Site	Epidemoid N=73	Undifferentiated N=23
Lung	22%	61% (')
Pleura	14	30
Liver	18	43(')
Bone	8	30(')
Kidney	7	22(')
Adrenal	7	4
Brain	<2	<2
Stomach	<3	<1

(') significant at p<0.001

Interesting data were reported by Quint et al. They looked for metastases in patients presenting initially for diagnosis and treatment. Of 838 patients seen between 1982 and 1993, 147 or 18% had distant metastases (M1).
Overall several upper third tumors had infra-diaphragmatic spread to the liver and adrenals. In the data from Sons et al., distant metastases were more frequent in

tumors of the upper third (87.5%) and 81% in the tumors of lower third. For the middle third, it was 60%. The histology type of adenocarcinoma had more liver metastases, while epidermoid tumors had more lymph node metastases (Table 9.11 and 9.12).

Table 9.11 - Cancer of the Esophagus
Metastases according to location of Tumor
Data (abridged) from Quint et al. (°)

Site	Upper N=6	Mid N=35	Lower N=106	Total N=147
Cerv-SuCl No	0	37%	12%	18%
Abdom.LyNo	0	37	34	33
Lung	50	11	8	10
Liver	17	9	36	29
Bone	17	11	7	7

(°) only histologically proven cases

No obvious difference is seen when the data of Quint in patients at first presentation are compared with the data obtained from autopsy studies. It is well known that esophageal cancer kills more by locoregional spread within the mediastinum hindering and influencing the feeding of the patient than by its distant metastases.

Table 9.12 - Cancer of the Esophagus
Metastases according to Histology
Data (abridged) from Quint et al.

	Adeno N=105	Epider N=35	Undiff N=6	Small N=1
Cerv-SuCl No	13%	31%	17%	--
Abdom.LyNo	29	46	33	(1)
Lung	9	11	33	--
Liver	37	9	0	0
Bone	8	6	17	0

Metastases at autopsy are seen by the pathologists, while they are found by imaging in living patients. Imaging plays an important role as it does in all oncology patients. Almost three quarters of the metastases are found through CT of the chest and/or of the abdomen and 25% at surgery, demonstrating that the other methods used, either systematically applied or not, have a very low yield and should not be utilized routinely (Table 9.13).

Table 9.13 - Cancer of the Esophagus
Method of detection of metastases (N=147)
Data of Quint et al. 1995

Physical Examination	5 (3%)
Imaging	
CT chest / abdomen	102 (69%)
Bone scan	9 (6%)
CT head brain	3 (2%)
Chest Radiograph	3 (2%)
At surgery	37 (25%)

In recent years, PET-scan with 18-fluoro-deoxyglucose has been introduced to detect metastatic sites undiscovered by the usual methods. Luketich et al. found 70 distant radiographically occult metastases in 39 scans. It mainly concerned small liver metastases (23/70) and several mediastinal or distant lymph node metastases. Several authors have reported similar data, revealing that this imaging is more sensitive than CT for revealing regional and distant metastases, although some false-negative and -positive have been seen (Flamen et al.).

Overall, it can be concluded that the most frequent distant metastases are located in the liver, the lungs, the adrenals and kidney. The involvement is positive in 30 to 50% for the lung and liver, but only 15 to 20% for the adrenals and kidney. All other sites are involved in less than 10% of the cases.

The multiplicity of metastatic sites is much less frequent than in other cancers. Less than 4 sites are involved in 57% of the patients, while 43% have more than 3 sites (Anderson et al.). This contrasts with other tumors such as breast and prostate where there will be multiple sites involved in more than 70% of the patients.

Pleuro-Pulmonary Metastases

Although autopsy studies reveal that half of the patients have lung metastases, a study specifically addressing the subject is not at hand.

Examining prospectively the lungs of 16 patients, Soares et al. observed pulmonary tumor embolism in 7 cases, with involvement of lymphatic vessels in all of them, associated with arteriolar or/and arterial involvement in 2. Dyspnea had been present in 3 patients and the clinical picture of subacute cor pulmonale was present in two patients.

Although the metastatic pattern mentions pleural metastases in 30% of the patients, no report has specifically addressed this metastatic site for esophageal cancer. Jiao et al. reported recently on a prospective study concerning the cytology of the pleural cavity in operatively treated cases. They found positive cytology in 18.8% of the 48 patients. Neither stage, size, location nor tumor length could be correlated. Histology was squamous cell in 8 and small cell in 1.

Bone Metastases

Several authors have stressed the low frequency and the fact that, except the spine, there are no particular preferential sites. Metastases in the long bones and in the extremities are not rare in this cancer.

An incidence of about 5% was noted in 1909 treated patients. Remarkable is that in 75% there was only one metastatic site. (Goodner et al.). The distribution within the skeleton is depicted on fig. 9.6.

Theoretically, the dorsal spine can be invaded from a posterior mediastinal node.

Of 22 patients with bone metastases, 19 were in the spine and in 13 of the 22, or half of the patients, there was only one site involved. (Adenis et al).

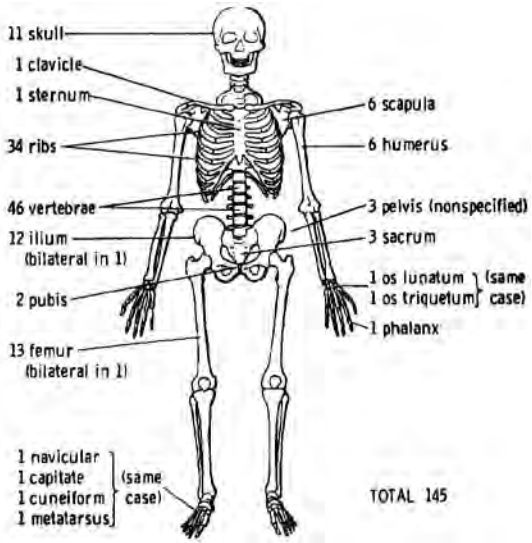


Fig.9.6 - Location of metastasis in bone in 100 patients (Goodner et al., with permission)

It is worth mentioning that a number of type 1 or revealing metastases have been reported, three cases by Siame et al. These involved the thoracal spine, the distal femur and there was a spinal cord compression due to osteolysis of C2-C3. Another type 1 presentation was reported by Cuomo in a patient with a lower third cancer revealed by a scapular metastasis.
One patient with a metastasis in the patella occurring during follow-up was reported by Ashby. A number of acral metastases have been reported (Table 9.14).

Table 9. 14 - Cancer of the Esophagus
Acral Metastases Reported

Levack 1983	Le. middle finger (Revealing)
Haas1988	Ri. little finger, proximal phalanx
Umebayashi 1998	Ri. index finger, distal phalanx
Tasaka 1999	Le. little finger, distal phalanx
Houston 2000	Le. .ring finger subcutaneous

Metastases to the Bone Marrow

O'Sullivan et al. studied 50 consecutive patients with cancer of the esophago-gastric junction and found that micrometastases were found in the bone marrow of 24 of the 27 patients examined. This must be compared with the involvement of the iliac bone in only 4 of 27 patients studied.
A similar study was reported by Thorban et al. They found CK-positive (Cytokeratin) cells in the iliac crest-bone marrow in 36% of 38 patients treated curatively and in 48% of 33 patients treated palliatively. The authors concluded only on a possibility for increased hematogenous metastases, but data are poor.
It is probable that in many patients there is a diffuse microscopic spread of the tumor, not immediately visible at any examination. The follow-up period is, however, always too short in the reported series.

Central Nervous System

Brain metastases have rarely been reported in patients with esophageal carcinoma.
In 334 patients, there were only 12 patients with subsequent brain metastases, or only 3.6%. It concerned an adenocarcinoma in 10 patients and an epidermoid in two. All except one were male patients. Two had a cerebellar location (Gabrielson et al.).
Another patient with a cerebellar metastasis manifesting as a cerebral hemorrhage was reported by Harrigan et al. Nguyen reported on a patient (M64) presenting with hydrocephalus due to cerebellar metastasis.
The report of Schuster et al. on two patients with a solitary metastasis to the pineal gland stands out as unusual. This a very rare metastatic site, as discussed in Part I.

A comatous patient with hemiparesis (M57) was brought to Emergency. CT revealed a subdural hematome confirmed at urgent surgery, but with malignant infiltration of the dura mater. The patient's condition progressively deteriorated and at autopsy, a metastasized esophageal carcinoma was discovered (Vonofakos et al.).
Sudden and rapid onset of blindness due to meningeal metastases as revealing symptom of an esophageal cancer was described by both Tearr et al. and by Civantos et al. Another lately occurring case was reported by Irie in a young female patient of 45.

Metastases to the Stomach

As already discussed above, spread to the stomach can be due either to intramural or submucosal lymphatic spread, to contiguous invasion by the exten-ding tumor of the lower third or by true hematogenous metastases. Spread from paragastric lymph nodes has also been reported as being a possibility.
In a series of 35 patients, Saito et al. pointed to the fact that intramural metastases, lymphatic invasion and lymph node metastases were the most frequent cause. Moreover, stomachal involvement was found in 25 patients only at autopsy. True stomachal metastases were in fact not observed.
According to a literature review up to 1986, metastases described as gastric are seen in 2 to 15% of the patients (Glick et al.). Reporting on a small number of cases, several authors also concluded that the lymphatic and intramural pathway were implicated.
One case of metastasis in a giant gastric ulcer was reported by Attorjay et al.

Metastases to the Small Intestine

We are aware of only two reports. A metastatic tumor involving the jejunum 11 months after surgery was found in a male patient of 56.
Another report concerned a metastasis in the proximal jejunum about one year after surgery in a man aged 65 (Wang et al.).

The metastatic pathway can be discussed, but is most probably hematogenous.

Ophthalmic Metastases

Being a rare event in several cancers, it is also rare in esophageal cancer. Only a few cases have been reported, but as quite a number were revealing metastases, there is probably a reporting bias, in view of the special diagnostic circumstances (table 9.15).

Table 9.15 - Cancer of the Esophagus
Reported Ophthalmic Metastases

Author	Pat	Site of Metastasis
Pusateri 1987	M55	Oculomotorius muscle
Mooy 1990	M59	Choroid (Revealing)
Parikh 1993	M35	Choroid (9mo after surgery)
Cangiarella 1996	F51	Retina (Revealing)
MacDonald 1997	M56	Choroid (Revealing)
CaillezTomasi'97	M71	Choroid bil. (1yr after surg.)
Caroli 1998	F73	Choroid
Collins1999	M47	Orbit (adenocarcinoma)
Oh 2000	M56	Orbit(Revealing) (Adenoca)

Metastases in the Kidney

One case has been reported by Steiner et al. in a women treated previously by surgery and radiochemotherapy. Two other cases were reported by Grise et al, occurring during follow-up after surgery. In the autopsy statistics, the kidney is involved in less than 10% of the cases.
A renal tumor turned out to be a metastasis of an unknown epidermoid esophageal cancer in a M81 (Marsan et al.).

Metastases to the Skin

Up to 1997, only 4 cases with skin metastases should have been reported. One type 1 metastases over the scalp was published by Terunuma in a man of 64.
Most probably this is an underreported metastatic site.

Metastases to the Head and Neck

This is not an uncommon site for esophageal carcinoma. It has been described within several sites (Table 9.16).
All patients reported with a H&N metastasis, were men. It would appear that the esophageal cancers share the propensity to metastasize within the mandible, with hepatocellular carcinoma.
New primary tumors in the head and neck region must be considered in the differential diagnosis.

Other Metastases

A metastasis in the shaft of the penis was reported by Gupta, occurring within a month of the diagnosis of the primary.
A large revealing splenic metastasis of about 8 cm in a man of 80 was the revealing sign of a mid-third cancer of the esophagus (Rudelli et al.).
Extensive destruction and replacement by tumor was found in both adrenals at autopsy in a patient (M76). He acutely deteriorated in the postoperative phase, but the adrenal involvement was not suspected (Hasan et al.).

Table 9. 16 - Cancer of the Esophagus
Head and Neck Metastases Reported

Author	Pat	Site	Interval
Sokolovsky 1986	M30	Gingiva	Revealing
Tideman 1986	M59	Maxilla Le	Revealing
Jones 1989	M54	Mandible Le	Revealing
Anderson 1990	M61	Mandibula Re	Revealing
Zappia 1992	M49	Maxill.Sinus	Revealing
Inui 1993	M74	Praeauricular muscle	4 mo
		Literature review cites 12 cases at several sites (')	
Plath 1996	M64	Mandibular fracture	3 mo
Koyama 1997	M54	Mandibular bone	Revealing
Ide 1997	M63	Gingiva	8 mo
		Literature review cites 8 cases, but no data are given	

(') 4 of them were revealing type 1 metastases. Ten of them concerned the mandibula and one was located in the tongue.

Left-sided abdominal pain, loss of appetite and weight loss led to a CT-diagnosis of a pancreatic mass. FNAC disclosed a squamous cancer and further exploration led to the diagnosis of a primary in the distal esophagus (Kolbusz et al.).

Overall Lessons

Carcinoma of the esophagus most frequently kills by intrathoracal extension and invasion, impairing the nutritional status of the patient. Distant metastases seem not to have much time to develop as they do in other cancers.

METASTASES from CANCER of the STOMACH

In spite of its relatively high though declining incidence, the metastatic pattern of gastric cancer is in fact poorly documented. Only a few autopsy data have been published.
Regional lymph node metastases is on the contrary extensively documented, due to the diligence of Japanese collegues confronted with the epidemics of this cancer in their country.
Stomach cancer can spread along different pathways (Table 9.17). They first spread within the stomachal wall, intramurally sometimes towards the duodenum and/or the esophagus. As the stomach is adjacent to several other organs, contiguous invasion is possible.
Lymphatic spread towards the regional lymph nodes has been extensively studied and documented. Distant

or true metastases are well known but either are relatively infrequent or most probably are poorly documented. Quite a number of revealing metastases have been reported at several different sites.

Table 9.17 - Cancer of the Stomach
Pathways of Metastatic Spread

1. Intramurally (longitudinal)
2. Contiguous invasion
3. Lymphatic spread to regional nodes (and further)
4. Hematogenous Metastases

Overall Autopsy Data

A well documented series of 85 patients was reported by Wisbeck et al. (Table 9.18). No treatment had been given to 24 patients.

Table 9.18 - Cancer of the Stomach
Distant Metastases at Autopsy (N=85)
Data of Wisbeck et al.

Mediast.Nodes	18.8%	Bone	18.8%
Peritoneal	47.0%	Heart-Pericard	4.7%
Liver	38.8%	Brain	none
Lung	34.1%	Meninges	2.3%
Pleura	24.7%		

The data permit the conclusion that stomachal cancer remains rather locoregional and usually produces distant metastases only in the first organ the circulation reaches, which is likely to be the liver or the lungs. Metastases in bone is low compared to other cancers, and metastases in the brain are rare.

Metastases have also been correlated with the histological type, according to the Lauren classification. Two series have been published, but the data are not completely concordant. We have summarized the data on tables 9.19 and 9.20.

Table 9.19 - Cancer of the Stomach
Metastases according to Histology Type (N=77)
Data of Duarte et al. 1981

Site	Histology Type Intestinal N=30	Diffuse N=47
Nodes		
Abdominal	86.7%	85.1%
Mediastinal	33.3	21.3
Cervical	3.3	4.2
Parenchymal		
Liver	60.0	29.8 (‘)
Lung	33.3	42.6
Peritoneum	23.3	46.8(‘)
Adrenal	6.7	21.3
Ovary (“)	6.7 (2/12=16%)	19.1(9/22=41%)
Pancreas	6.7	14.9
Kidney	3.3	10.6
Spleen	3.3	10.6

(‘) significant at p<0.01
(“) recalculated for the female patients(N=34)

Table 9.20 - Cancer of the Stomach
Metastases according to Histology Type (N=104)
Data of Weiss et al. 1993

Site	Histology Type Intestinal N=54	Diffuse N=40
Liver	55.6%	2.5%
Lung	13.0	7.5
Peritoneum	25.9	70.0
Adrenal	13.0	12.0
Ovary(“)	3.7	10.0
Bone (Spine)	22.2	40.0
Lymphang.Pulm	16.7	32.0
Pleura	13.0	26.0

(“) the number of female patients was not given

The overall trend is fewer liver and lung metastases in the diffuse type, but more peritoneal and abdominal organ metastases.

We are not aware of other data according to gender and age, or even according to the site of the primary within the stomach.

Peritoneal Spread

Autopsy data show that peritoneal spread through invasion of the serosa occurs in about one quarter of patients. Hardly discussed from an anatomical point of view, it is only recently that the instauration or at least the attempts or even trials for aggressive treatments of peritoneal carcinomatosis (PC) has led to new insights in this dreadful and previously as fatal considered clinical situation.

A landmark in treatment evaluation, the staging method and recently applied in a multicenter French study has been proposed by Gilly et al. (Chapter 3).

The study collected 370 patients with a non-gynecological malignancy in the period 1995-1997 and reported a good deal of interesting demographic and anatomic data. In more than two-thirds it concerned digestive cancers and included 125 cases of stomach cancers, of which 58.5% were already with PC at first presentation. In 57.5% the PC was found in stage III-IV. The mean age of the PC- patients was 60.5 yrs (range 21-96).

Lymph Node Metastases

The pathways of lymphatic spread to the regional nodes has been studied extensively by Japanese authors. The flow and anatomy of the lymph nodes has been codified by the Japanese society for gastric cancer surgery (fig.9.7, table 9.21 and 9.22).

Extensive data are available on the incidence of involved nodes within each lymph station, according to the site of the primary, the histology type, the depth of invasion and the size of the tumor. We will only summarize the results, as they have been reported for mid-stomachal cancers (Wu et al.).

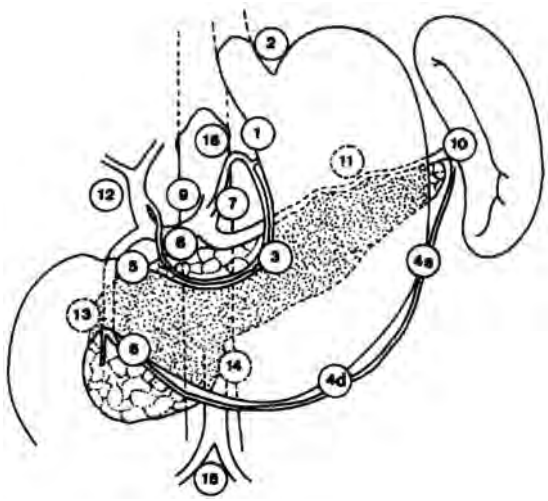


Fig.9.7 - Codification of the regional lymph nodes of the stomach, according to the Japanese Rules for Gastric Cancer . From Wu et al. with permission. The code numbers are on Table 9.21.

Data according to gender and age reported by Adachi et al., showed no significant differences in 240 patients. Lower-third tumors had much less LNM at level III than the others, but slightly more at levels I and II.

The data of Namieno et al. which relate to early gastric cancer, a 'type' increasingly being detected due to screening for gastric cancer, are interesting. We summarize the data in table 9.23.

The frequency of lymph node involvement is strongly dependent on the depth of invasion of the cancer.

Reviewing literature data, Lehnert et al. found that when mucosa only was involved, lymph node metastases occurred in only 60/1,447 or 4.2%, while for submucosal involvement, the incidence was 16.8% (253/1509).

Table 9. 21 - Cancer of the Stomach
Designation of Regional Lymph nodes
Japanese Rules for Gastric Cancer Study

Level I	1 Right paracardial
	2 Left paracardial
	3 Lesser Curvature
	4 Greater Curvature
	5 Suprapyloric
	6 Infrapyloric
Level II	7 Left Gastric Artery
	8a above common hepatic artery
	8p behind common hepatic artery
	9 Celiac axis
Level III	10 Hile of the Spleen
	11 Splenic artery
	12a Hepatic artery
	12b Common Bile Duct
	13 Retropancreatic head
	14 Mesenteric Root
	15 Middel Colic Artery
	16 Para-Aortic

Table 9.22 - Cancer of the Stomach
Grouping of Regional Lymph nodes
Japanese Rules for Gastric Cancer Study

Group	Location of Cancer		
	Upper	Middle	Lower
N1	1,2,3,4	1,3,4,5,6	3,4,5,6
N2	5,6,4,8a,9 10,11	2,7,8a,9, 10,11	1,7,8a,9
N3	8p,12,13,14	8p,12,13,14	8p,2,10,11 12,13,14
N4	16	16	16

Table 9.23 - Early Cancer of the Stomach
Correlation Pathology with Lymph node involvement
Data on 1137 patients (Namieno et al.)

Site/Feature	Most frequently involved station(s)
Cranial Third	3
Middle Third	3 and 4
Lower Third	3, 4, 5 and 6
Lesser Curvature	3
Greater Curvature	3, 4 and 6
Anterior Wall	3 and 4
Posterior Wall	3 and 4
Only Mucosa	3
Submucosal involv.	3, 4, 5, 6, 7
Elevated Type	3 and 4
Depressed Type	3, 4, 5, 6
Intestinal Type	3, 4, 5, 6
Diffuse Type	3, 4, 5, 6 and 7

1. Extension of the tumor either to the upper or lower third produced a variable incidence of lymph node metastases (LNM); 19 to 58% at the lesser curvature (3), 7 to 35% at the greater curvature (4), 12 to 35 at left gastric (7) and 2 to 26% above the common hepatic artery (6a).
2. Tumors growing more upward had more LNM at the splenic hilum (10), 12% and when tumors involved the whole circumference it reached 17%.
3. The depth of invasion increased the LNM metastases from 12% when mucosal, 44% at muscular invasion and to 72% when the serosa is invaded.
4. When the serosa is invaded, LNM at N3 and N4 levels are increasingly observed, but only in 5-10%.
5. Laurens' histology: Diffuse type has overall a much higher LNM rate of 50%, compared with only 38% in intestinal type.
6. The LNM rate increases with tumor size; 32% for tumors less than 4cm, 52% for tumors between 4 and 8 cm and more than 70% for tumors larger than 8 cm.

Distant Metastases

There is a certain correlation between the depth of invasion of the cancer and the later incidence of distant metastases. With a t.1 invasion (intra-epithelial), only 0.2% had subsequent peritoneal metastases, while at t.3 (penetrating the serosa), the incidence was 34%. The data for distant metastases were resp. 0.7% and 13.4% (Ikeguchi et al.).

The influence of positive lymph node invasion on subsequent metastases was analysed by Maehara et al. in 323 patients. Local recurrences, liver and lung metastases were much more frequent in patients with positive nodes. Several other metastases were seen in the latter group (Table 9.24).

Table 9. 24 - Cancer of the Stomach
Site of Recurrences after surgery (N=323)
Influence of Lymph node - Serosa Invasion
Data of Maehara et al.

Site	No invasion N=110	With Invasion N=213
Local	11.8%	10.8%
Peritoneum	21.8	18.7
Lymph node	11.8	10.8
Liver	5.4	14.5
Lung	1.8	4.2
Bone	--	3.2
Brain	--	3.8
Skin	--	2.3
Ovary	(N=1)	(N=2)
Unknown	6.3	12.6
Total	44.5%	64.7%

We are not aware of any report reviewing the distant metastases of gastric cancer. As far as the autopsy series concerns, the rate seems much lower than for other cancers. Most reports concern cases where gastric cancer was revealed by the appearance of any metastases (type 1), and is hence probably biased, as several metastases should occur in follow-up.

The symptomatology of distant metastases during follow-up is probably obscured by the intra-abdominal spread and other metastases and declining general status.
We recently found interesting data in the report by Maehara et al. concerning the occurrence of metastatic disease after gastrectomy in 939 patients, with a median follow-up length of 24.3 months. Hematogenous recurrence occurred in 70 patients of the 130 who died. It concerned the liver in 43 (33%) patients, the lung in 16 (23%), bone in 4 (5.7%) and brain in 7 (10%).

Pulmonary Metastases

Although the incidence of pulmonary metastases is quoted as 30 to 40% at autopsy, we have not found any report addressing this type of metastases.
A case (F36) of cor pulmonale due to tumor cell micro-emboli in more than 50% of the pulmonary vasculature, revealed only at autopsy a gastric carcinoma at the pylorus with lymph metastases, left adrenal and both ovaries (Hirata et al.). A similar patient (F78) had been reported previously by Kupari et al. and recently by Montero et al.

Bone Metastases

There are very few reports on bone metastases in gastric cancer. Its incidence seems to be low at least in the autopsy data as reviewed by Stankovic et al. (Table 9.25). All these data are probably autopsy-data and are of the pre-scintigraphy era.
The overal distribution in the skeleton was reported by the same authors (Table 9.26). Some patients had more than one localisation. In view of the preponderance of spinal metastases, contiguous invasion from retrogastric nodes would seem likely.

Table 9. 25 - Cancer of the Stomach
Incidence of Bone Metastases
Literature Review by Stankovic et al.1969

Author	N	Percent
Copeland 1923	537	1.3%
Jenkinson 1924	309	2.5%
Borrmann 1926	147	2.7%
Geschikter 1939	750	0.9%
Walther 1948	711	5.6%
Abrams1950	119	11.0%
Fraenkel 1955	39	20.5%
Stankovic 1969	447	8.5%

Table 9. 26 - Cancer of the Stomach
Anatomic Sites of Bone Metastases (N=38)
Data of Stankovic et al. 1969

Vertebral Column	32	Sternum	2
Rib	6	Sacrum	1
Skull	5	Pelvis	1
Femur	3		

A similar distribution was reported by Yoshikawa et al. They mention 4 metastases in the humerus, 4 in the femur, 1 in the ulna and 2 in the scapula.
One would expect that the advent of the more sensitive detection method of isotope-scintigraphy would have yield a higher incidence. We are aware of only one dedicated report. Reviewing 234 patients, Choi et al. observed bone pathology in 106 or 45.3%. This is about 3 to 4 times the incidence as quoted by the autopsy studies. We have summarized the data on Table 9.27. A single lesion was observed in 12 (11.3%) of the metastatic lesions. On the other hand, 6 patients had the typical 'super-scan', correlating with disse-minated bone metastases.

Table 9. 27 - Cancer of the Stomach
Incidence of Bone Metastases on Scintigraphy
Data of Choi et al. in 234 patients (')(°)

Spine	110	Sacrolliac	12
Skull	36	Femur	51
Rib	97	Humerus	10
Shoulder	28	Sternum	7
Pelvis	71	Tibia	5

(') 167 lesions in 106 patients
(°) About 90% of the patients were 'advanced' stages

These data clearly show that the incidence of bone metastases in gastric cancer is much higher than usually stated. Unfortunately, no confirmatory series are at hand.

At radiology, the metastases are usually osteolytic. Some cases with an osteosclerotic aspect have been reported (Carstens et al.).
One case has been reported of a osteolytic metastasis within os hamatum (carpus) of a previously resected gastric adenocarcinoma (Craigen et al.) and another in the calcaneum (Berquist et al.) as first sign. The rare metastatic site of the patella was reported in a gastric cancer by Kaneko et al. and in the distal tibia by Tadross et al.

Bone marrow involvement has recently received some attention, as being in fact a precursor of bone metastases and initiator of osteolysis. According to Jauch et al. who studied 180 patients, positive cytology was obtained in 95 cases or 53%, in early curatively operated patients and in advanced cases as well. This is indicative of an early dissemination of the neoplastic disease, but follow-up data were not reported.

Metastases to the Central Nervous System

A review of 3320 patients with gastric cancer, disclosed only 24 patients who had developed brain meta-stases (York et al.). The diagnosis was made in 19 during follow-up and in 5 only at autopsy. The metastasis was single in 45% and multiple in 55%, and in all patients multiple other sites were involved. When it could be determined, the mean interval was 9 months (1-23 months). Data on cerebral sites are not given.
Kim et al. reported on 8 cases. The interval ranged from 1 to 33 months, with a median of 14 months. Two concerned the cerebellum, while in the other the involved sites were frontal, temporal or parietal. Only one had more than one metastasis.
Without giving the total number of gastric cancers treated, Kaskura et al. reported recently on 11 patients. The mean interval was 9.6 months, with a median of 5.7 months. The brain metastases were solitary in 4, multiple in 6 and hemorrhagic in one. It concerned only 2 female patients.

Reporting on a case (M35) presenting with a metastatic subdural hematoma, Bergmann et al. found 6 other cases from a stomachal cancer in the literature.
On the other hand, meningeal carcinomatosis is not uncommon in gastric cancer. The pathway is probably direct invasion through the intervertebral spaces from lymphatic permeation. Several cases have been published where the meningitis was the revealing situation of an occult gastric cancer. We have collected them on table 9.28, but we refer also to Chapter 5.

As was discussed in the chapter on leptomeningeal metastases, stomach cancer is a frequent primary to think of. Of 13 cases with CNS-involvement, Kim et al. reported on 5 cases. Their interval from first treatment to metastases ranged from 2 to 7 months and 3 of them were female patients.
A parasellar metastasis was the first sign of a stomachal cancer found at autopsy as the patient (M57) died 4 weeks after presentation (Bitoh et al.).
One case of revealing metastasis to the pineal gland has been reported (Joyner).

Table 9. 28 - Cancer of the Stomach
Case Reports on Leptomeningial Metastases

Author	Pat	Sign	
Pissas 1981	F47	Slow progressive story	R(°)
Bigner 1984	M66	Dementia	R
Bigner 1984	M76	Confusion, periph.neurop.	R
MacCrary 1986	F60	Sudden blindness	R
Groves 1991	M52	Deafness, diplopia	A
Birouk 1993	M53	Cauda Equina syndrome	R
Patri 1997	M64	Disorientation, walk probs	A
Deeb 1997	M53	Vomiting, diplopia	R
Mouallu 1998	F67	Headache, blurred vision	FU
Morgan 1998	M69	Headache, sudden deafness	R
Scully 1999	M53	Widespread metastases	R

(°) R: revealing metastases; A: diagnosis only at autopsy; FU: found during follow-up.

Recently, a patient (F51) was reported who presented with a symptomatology of C3 sensory quadriplegia due to an intramedullary lesion of 2.5 cm at C1-C2 level. Surgery revealed a metastasis from a poorly differentiated adenocarcinoma, subsequently confirmed at gastroscopy. She, however, had also a small brain metastasis in the frontal lobe (Taniura et al.).

Metastases to the Female Genital Organs

The link between stomach and ovary is an historical one and has received the eponym of Krukenberg tumor, although the cases reported were not correct.
However, there are almost no reports addressing the incidence of ovarian metastases from gastric cancer. Hirono et al. reported on 30 autopsied women and found 25 cases with metastases, or 83%. Bilateral involvement was seen in 20 of the 25. Peritoneal spread was seen in most of the cases.
In 690 consecutive (female) patients, Kim et al. found ovarian metastases during follow-up in 32 patients, or less than 5%. This is probably a figure closer to reality. Most were symptomatic. The median interval between first surgery and ovarian metastases was 14.7 months (range 3.6-39 months), but 30/32 occurred within 3 years. The metastasis was confined to the ovary in only 6 patients, while it was part of more or less extensive diseases in the others. Results of any autopsy were not reported.

Metastases in the endometrium from gastric cancer is rare. We are aware of four reports each presenting a patient in whom endometrial abrasion yielded signet cells pointing to an occult gastric carcinoma.
Intraluminal spread through the Fallopian tube has been considered, as well as retrograde lymphangitic or hematogenous (Stemmerman et al.).

Many more cases have been reported with metastases in the uterine cervix. All the reports concerned revea-

ling metastases. It is obvious that metastases in the cervix during follow-up have not the same attention, so that its incidence is unknown.
The literature was reviewed in 1990 by MacGill et al. They found 30 cases, all confirmed as gastric cancer. In 2 cases, cervical biopsy or cytology was negative, but other signs pointed to the stomach. In the meantime, 20 other cases have been reported (Table 9.29). Usually only the endometrium was involved, but in a few cases the myometrium also (Kim et al.).

Table 9.29 - Cancer of the Stomach
Cases revealed by Metrorrhagia
Literature cases since 1990

Sommerville 1991	F39 during pregnancy
Imachi 1993	16 cases (20-59 yrs, 3 postmenop.)
Mambrini 1995	F26 advanced cancer
Pasini 1995	F53 postmenopausal bleeding
Matsuura 1997	4 cases (age 37-44 yrs)
Franchi 2000	F38 routine Pap-test positive

We are also aware of one case of metastases to the clitoris (Ahmed et al.).
Up to 1991, 15 cases of metastases to the breast from a stomachal cancer were reported (Hamby et al.). It was bilateral in three cases at least. They were, at least in five cases, the first sign of the stomachal cancer. Later, a case presenting with cutaneous inflammatory infiltration as metastases from a previously surgically treated gastric cancer was published. This case was probably more likely to be a type of skin metastasis (Cavazzini et al.).

Metastases to the Muscles

This rare metastatic site has been the object of several reports, even as revealing metastases of gastric cancer. Local swelling, pain and hinderance to certain movements were the presenting signs.

Table 9. 30 - Cancer of the Stomach
Metastases in Muscles - Literature Reports

Author	Pat	Site of Metastasis	
Treves 1979	F74	M.Iliopsoas	R(')
Obley 1983	M54	Paraspinal, shoulder, thigh (M.O.)	R
Rosenbaum 1984	M54	Shoulder, paraspinal, Pelvic muscles (M.O.)	R
Porile 1990	M65	M.Sartorius	R
Allen 1992	M71	M.Iliopsoas + Hip-Thigh (M.O.)	R
Toillon 1994	M58	M.Gemelli	FU
Narvaez 1998	M49	M.Iliopsoas + Paravertr	R
Pestalozzi 1998	M70	M.Gastrocnemius	R

(') R: revealing metastasis, M.O.: Myositis Ossificans
FU: at follow-up

Quite a number were diagnosed first as 'myositis ossificans' due to some calcification at radiology or at CT. It is striking that the M.Iliopsoas is the most frequent involved site. Retroperitoneal lymphatic spread must be considered as the most probable pathway (table 9.30). From the reports, it is not clear if it concerned a lymph node invasion or true metastases (see Chapter 7).
Remarkable is the relatively high age of these patients.

Head and Neck Metastases

Several cases have been reported, occurring almost all as revealing metastases (table 9.31).

Table 9. 31 - Cancer of the Stomach
Head and Neck Metastases Reported

Author	Pat	Site of Metastasis	Interval
Lund 1968	F63	Gingiva	Simult
Weitzner 1968	M60	Tongue	6 months
Passmore 1981		Tonsil	
Gallo 1992	M68	Tonsil bilateral	Reveal
Owa 1995	M61	Ethmoid (')	18 mo
Pardal 1995		Larynx	
Florio 1995	M66	Palate	3 mo
Benito 1996	M42	Tonsil	Reveal
Ozturk 1997	M73	Parotid gland	3 yrs

(') we question this case as he was a furniture worker, so that adenocarcinoma within the ethmoid is difficult to differentiate from a gastric adenocarcinoma

Ophthalmic Metastases

There are only two reports on intra-ocular metastases (Karnad et al. and CaillezTomasi et al.). Intra-orbital muscle metastases are more frequentthan in other cancers. One was a revealing case (Van Gelderen), but in the other case, it was part of wide-spread disease. Küchle et al. reported a gastric cancer patient diagnosed after presentation of metastasis in the conjunctiva and eyelid. Three other cases have appeared in the literature.

Metastases to the Digestive Tract

A very rare situation caused by metastasis is achalazia, dysphagia for both solids and liquids, with regurgitation, chest pain and aspiration. The few reported cases were shown to have high gastric invasion with extension towards the cardia and extensive perineural invasion of the esophagus, without any significant tumoral invasion or obstruction. Most are gastric cancers.
Reporting on 7 patients, Tucker et al. established three clinical criteria to distinguish the secondary achalazia: advanced age (>50 yrs), symptoms less than one year and a marked weight loss (more than 15 pounds).
The description in the case of Shulze et al. is typical: a hyperemic mucosa and thickened wall at endoscopy, with at microscopy a mucosa displaced by an adenocarcinoma. At the cardia, the tumor infiltrated through the muscularis and even as far as the attached striated diaphragmatic muscle.

Metastases in the duodenum can be explained either

by longitudinal intramural spread, either as contiguous invasion or as true hematogenous spread. Elmes found 12 patients with duodenal involvement in a series of 112, or about 10%. In almost all cases, the initial lymphatic intramural spread was the cause. A series of 5 cases was reported by Raijman et al.; these corro-borated the findings of Elmes and others.

Metastases to the gallbladder would appear to be rare, as only two reports have appeared.
Publications specifically concerning the pathology of liver metastases are rare. A small autopsy series on 80 patients showed that 38 or 47.5% had liver metastases, a figure similar to the data mentioned in the previously cited larger autopsy series (Rhomberg et al.). The frequency was highest in the intestinal type histology, compared with diffuse type (68% vs 18%.

Metastases in the colon from gastric cancer are very rare. One case mimicking Crohn's disease was reported by Katon et al., while two other cases presenting as colonic polyps as first manifestation have been reported (Metayer et al. and Ogiwara et al.). Other reports are unavailable as they have appeared in the Japanese literature.

Having reviewed 996 records, Jang et al. found intestinal metastases in 23 or 2.3%. The ascending colon and the rectum were the most frequently involved site (table 9.31bis). They distinguished 3 patterns of wall thickening, of whom the second was the most frequent:

type 1 : preserved wall-layering pattern with predominant thickening of the outer low attenuation layer;
type 2 : a target pattern with predominant thickening of the inner enhancing layer, and
type 3 : a thickened wall of diffuse soft-tissue attenuation with loss of the layering pattern.

Table 9. 31 bis - Cancer of the Stomach
Site of Intestinal metastases (N=23/996)
Data of Jang et al.

Multiple Sites	15	65%	
Small and Large bowel	6	26%	
Terminal Ileum	4	Transverse	9
Other small intestine	4	Descending	5
Ascending Colon	13	Sigmoid	3
Cecum	6	Rectum	11
Appendix	3		

One case of submucosal metastases in the rectum occurring 5 years after surgery has been reported by Bayer et al.

Non-Regional Lymph Node Metastases

Cited in all textbooks is the occurrence of supraclavicular lymph node metastasis. We are not aware of any specific case reports or review on the subject.

Ghanekar has reported on a case (M75) presenting with an abdominal wall infiltrate and a large axillary mass, (probably secondary to the latter), one year after the gastrectomy.
An inguinal recurrent node metastasis was observed 4 years after gastrectomy in a M63. The patient also had a rectal cancer, but the authors concluded on immunohistochemical grounds to a metastasis from the stomach cancer (Morita et al.)

Other Metastatic Sites

Cutaneous metastases would seem not to be unusual. Several cases have been reported presenting with skin lesions as first sign. Located in the neck, the axillary region, the chest or abdominal wall, it can render the diagnosis rather difficult, due to its appearance as another more common skin lesion (Descamps et al.). One case with a metastasis in the subcutaneous tissue of the little finger was reported by DiSpaltro et al. A patient (M39) with extensive cutaneous metastases all over the trunk revealed a poorly differentiated adenocarcinoma with signet ring cells. Further investigations disclosed an small gastric cancer, but with bone metastases. Autopsy after a rapid downhill course, revealed widespread metastases except to the liver (Hashiro et al.) (see also fig.7.3).
Metastases in the thyroid gland from gastric cancer is very rare. Michelow et al. mention 4 cases in their overall series of 16 patients, but are aware of only two case reports (Yoshida et al.; Ok et al.).

A number of cutaneous revealing metastases have been reported (Charfeddine et al.).
Cutaneous recurrence after port-site or other surgery is well-known but is not discussed here.

Pericardiac metastasis or effusion from stomachal cancer is mentioned in series addressing malignant effusion. Three case reports are concerned (Moriyama et al., Pimentel et al. and Sakai et al.). In the latter case, the tamponade was the revealing sign of a gastric cancer associated with abdominal and mediastinal lymph nodes, as well as with pleuritis and lymphangitis carcinomatosa.
One occult cancer presented with cor pulmonale resulting from tumor cell micro-embolism (Cheung et al.).

One male patient with metastases in the urinary bladder seven years after surgery was reported by Saba et al. One revealing metastasis in the adrenal by Quinton et al. and four revealing cases of testicular metastases have been reported (Zuk et al. and Reinhardt et al). Another revealing case was reported by Ibara et al. in a man aged 35 disclosing an antral carcinoma.
Fitch has reported on a man (M72) who was operated for an ureteral metastasis causing renal obstruction, three months after surgery for a pyloric cancer.
Finally, one case metastatic to the penis was reported

by Karanjia et al. and one to the epididymis by Koiunuma et al. In a man (M58) presenting with a painless swelling in the right scrotum, this turned out to be a metastasis from an asymptomatic gastric cancer at the lesser curvature (Olesen et al.).

Several reports in the Japanese literature mention metastases in the spermatic cord. The reports were not available to us, except the recent one by Ota et al. describing a β-hCG elevation pointing to a scrotal metastases nine years after gastric surgery.

Causes of Death

Reviewing the records of 172 patients subjected to gastrectomy for early gastric cancer, after a median follow-up of 7 years, 6.4% died of recurrence and 7.6 of unrelated causes. With a operative mortality of 4.1%, 82% remained recurrence-free (Guadagni et al.) The most frequent recurrence was in the peritoneum, followed by liver metastases and lymph node recurrence at the hepatic pedicle.

METASTASES from ADENOCARCINOMA of the SMALL INTESTINE

Malignant tumors of the small intestine are rare. Four types can be encountered: the adenocarcinoma from the mucosa, leiomyosarcoma of the muscle layer, carcinoids from the neuroendocrine cells and the lymphomas. Only the first type is discussed here, as leiomyosarcomas will be discussed in the chapter on sarcoma and the carcinoids in Chapter 14.
Lymphomas are beyond the scope of this work.

Spread - Metastases

The literature on metastases from tumors of the small intestine is rather silent. We are not aware of any autopsy studies. The tumor metastasizes along the lymphatics to the mesenteric lymph nodes and along the veins to the liver. Duodenal and Heal tumors tend to metastasize to lymph nodes, while jejunal tumors tend to penetrate the serosa or disseminate in the peritoneal cavity. Extension to the peritoneum is not rare and is, as far as can be judged from the surgical series, an important cause of death.
Lymph node metastases as distant as the supra-clavicular have been reported.
Vuori is the only author who has extensively reported on the sites of distant metastases in 100 cases: liver 17%, lungs 3%, adrenals 3%, omentum 9%, peritoneum 19%, spleen 3%, para-aortal lymph nodes 20%, uterus and ovary 6%, urinary bladder 4%, and colon 4%.
We are not aware of any other literature series specifically describing distant metastases. We have brought together the scanty data from some small surgical series in table 9.32.

Table 9.32 - Adenocarcinoma of the Small Intestine
Data on Metastatic spread (')

Ebert 1953	15 duodenal adenocarcinomas: Nodal 7, liver 5, Peritoneum 4, lung 2, Bile duct 2, adrenal 1, pleura 1, marrow 1
Vuori 1971	100 patients with metastases: Liver 17, lungs 3, adrenals 3, omentum 9, peritoneum 19, spleen 3, paraaortal nodes 20, uterus and ovary 6, urinary bladder 4, colon 4.
Bridge 1975	43 patients jejunum 6/32 mesenterial nodes ileum 5/9 mesenterial nodes 1 case liver, peritoneum, retroperit.nodes cervix 1 case diffuse skin metastases
Ouriel 1965	65 cases (34 duodenum): il-jej: 6 unresectable, because liver duodenum: 5/13 liver
Arai 1999	17 cases (elderly) Nodes 4, lung 2, liver 1, bone 1

(') nodes are ahead of mesenterial.

A few cases have been described involving metastases in the ovary (Niemec et al.). Synchronous ovarian metastases are the most frequent and pose the problem of differential diagnosis for the primary concerned (Young et al.). Overall ovarian metastases were the subject of most of the case reports (Table 9.32).
Bridge mentioned one patient (adeno-carcinoma) with metastases to the skin and to the uterine cervix. One case of ovarian metastases simultaneous with an ovarian gravidity has been reported by Rohde and one with bilateral ovarian metastases from a duodeno-jejunal adenocarcinoma (Loke et al.). Other rare cases are on Table 9.33.

Table 9.33 - Adenocarcinoma of the Small Intestine
Case Reports on Metastases

	Pat	Primary	Site	Interval
Ovary				
Gallup 1985	F52	prox.ileum	Le.Ov.	simult
Rohde 1986	F24	jejunum	Ri.Ov.	5 mo
Niemiec 1989	F41	jejunum	Le.Ov.	simult
Tsuruchi 1995	F49	jejunum	Ri.Ov.	simult
Loke 1997	F44	duod.jej	Bilater.	9 mo
Young 1998	Three cases - no further data			
Kilic 2000	F53	jejunum	Ri.Ov.	simult
Other				
McNamara 1937	??	??	Heart	??
MacCrea 1958	M	??	Penis	??
Askari 1981	M27	jejunum	Ri.Testis	simult
Alkins 1997	F52	jejunum	Ureter Le.	simult

METASTASES from Carcinoma of the APPENDIX

According to Uihlein and MacDonald, three malignant tumor types are described for the appendix

1. Carcinoids
2. Cystadenocarcinoma, mucinous

3. Adenocarcinoma, colonic type

Adenocarcinoid is regarded as a benign tumor.

There is extensive discussion in the literature on the distinction.

According to Deans, about all adenocarcinomas arise from pre-existing adenoma, as has been largely demonstrated in the colon.

Adenocarcinoma is easily identified, lacks mucin and is somewhat poorly differentiated.

Cystadenocarcinoma shows abundant extracellular mucin production and is well differentiated.

CRITERIA for diagnosis (Wolff & Ahmed)

1. Invasive growth into the submucosa through the muscularis mucosae layer of the appendix.
2. The bulk of the tumor has to be in the appendix.
3. When the tumor involves the serosa of the appendix and intraperitoneal spread from another tumor has to be considered, there has to be more histological growth near the appendix mucosa than near the appendix serosa.
4. The presence of coexistent adenomatous changes in the appendix near to or in association with appendiceal carcinoma.

The typical adenocarcinoma is mucinous, meaning that at least 50% of the lesion is composed of mucin and is well differentiated. A cystic or multicystic appearance is possible (mucinous cystadenocarcinoma). This is the so-called malignant mucocoele and is a cystic or sometimes multilocular tumor bordering on the columnar cells, sometimes associated with villi in the lumen.

Non-mucinous, colonic adenocarcinomas are less common and are indistinguishable from carcinomas occurring elsewhere in the large intestine (Carr et al.). This is still being debated in the literature. Their mucosa consists of acinar, tubular or papillary structures resembling the typical colonic tumor. It may occur either at the base or the tip, but most frequently at the base. Grossly it is grayish, polypoid or ulcerative.

Rarely signet ring adenocarcinomas have been described. They appear frequently in association with goblet cell carcinoids.

Metastasis from a gastric or ovarian primary should always be excluded.

Mucinous tumors may arise from adenomas, who by increasing loss the lymphoid component, and fibrosis of the lamina propria occurring, followed by further fibrosis of the submucosa and muscularis propria. A cyst can result, with a fibrous wall lined by neoplastic mucinous epithelium. Invasion is difficult to exclude so that it is mostly labeled 'of Uncertain Malignancy Potential' (UPA). According to Carr et al., they behave as low grade neoplasms and have a better prognosis than the classic adenocarcinoma

More recently the group at Johns Hopkins and that of the MGH[1] distinguish four types of appendiceal adenocarcinoma (Ronnett et al.).

1. Signet cell ring type with or without glandular or goblet cell differentiation;
2. Mixed signet ring cell and intestinal type;
3. Intestinal type
4. Typical colorectal type.

[1] MGH: Massachussets General Hospital, Boston

Spread

As the muscular wall is almost absent, penetration will be submucosal, and perforation is common as are peritoneal implants.

Peritoneal implants

According to Jacquet and Sugarbaker, two distinct patterns of dissemination to peritoneal surfaces have been observed.

1. Low grade cancers with a high content of extracellular mucin show a 'redistributed' spread. This means that large volumes will be found at some predetermined anatomic sites within the peritoneal cavity. This can be observed at surgery but also at CT, where small bowel and mesentery are surrounded but appear not to be infiltrated by the mucinous tumor. This could be correlated by the fact that these structures are in continuous movement. Tumorous masses accumulate within the greater omentum, the undersurface of the right hemidiaphragm, the right retrohepatic space, the pelvis and the abdominal gutters.

2. When moderate to high grade cells are released another pattern occurs: a randomly proximal (to the tumor of origin) distribution with cell implant where the cells initially make contact, with not much migration. This is due to the high adherence capacity. Tumor masses will be immediately adjacent to the loops of the small bowel and its mesentery. Further intracoelomic spread makes any resection impossible. Recent developments however pone aggressive surgery.

Lymph node metastases are noted in about 25 percent at presentation, more with the colonic-type adenocarcinoma than in Cystadenocarcinoma. Further spread results in involvement of mesenterial, peripancreatic, para-aortic and even mediastinal lymph nodes (Otto et al.)

The malignant tumors of the appendix have a certain propensity to spread within the peritoneal cavity and peritoneum, resulting in peritoneal implants all over the different organs such as colon and small intestine, but also over the different pelvic organs.

Cystadenocarcinoma is less virulent in spite of its ability to produce pseudomyxoma peritonei (P.P.). This is reflected in the grading as proposed by Sugarbaker:

Grade I: P.P. or Cystadenocarcinoma grade I.
Grade II: Mucinous adenocarcinoma, intestinal type adenocarcinoma.
Grade III: Signet ring adenocarcinoma, poorly differentiated adenocarcinoma.

There is some confusion in the literature as to the histological type leading to peritoneal dissemination.

A specific problem in female patients is the presence of ovarian metastases. An appendiceal carcinoma can present as a mass in the right fossa, masquerading as a primary ovarian tumor.
The concurrent presence of an ovarian 'mass' and an appendiceal tumor poses a diagnostic challenge, which is similar to the syndrome of normal sized ovarian cancer and the pseudomyxoma peritonei. In all these presentations the appendiceal primary might be overlooked.
Ronnett et al. collected 20 cases and established some clear guidelines for the diagnosis of an appendiceal primary:

- the appendiceal primary is an intrinsic mass, involving mucosa and wall;
- the ovarian metastasis are almost all bilateral and demonstrated histologic features incompatible and different from the presentation of primary ovarian cancers;
- If the ovarian tumor shows a histologic type similar to the intrinsic intestinal tumor, it should be almost certainly a metastatic one.

The involvement was bilateral in 80% (16/20). When unilateral only, the right ovary was affected.
The age ranged from 32 to 70 years, with a mean of 52 years. Most patients had vague low abdominal complaints, while others had symptoms of a process within the right fossa iliaca.

Table 9.34 - Adenocarcinoma of the Appendix
Presentations with Ovarian Metastases Reported

Author	Pat	Presentation	Side
Paone 1978	F28	Chron.pain Obstruct.	Bilateral
Merino 1985	F19	'Appendicitis'	Bilateral
Merino 1985	F45	Incr. abdom.girth	Bilateral
Merino 1985	F39	Ovarian mass	Ri.Ovary
Kashani 1983	F22	Low abdom. pain	Bilateral
Thorsen 1991	F47	Aspecific complaint	Bilateral
Thorsen 1991	F58	Weight gain in low.abd.	Ri.Ovary
Hull 1998	F34	Oligomenorrhea	Ri.Ovary
Sebire 2000	F29	Abdomal pain(')	Le.Ovary
McBroom 2000	F58	Abd.cramping	Ri.Ovary
McBroom 2000	F63	Abdominal pain	Ri.Ovary
McBroom 2000	F50	Vaginal bleeding	Bilateral

(') in the third trimester of pregnancy

Table 9.35 - Adenocarcinoma of the Appendix
Presentations reported as bladder cancers (after1975)

Author	Pat	Symptom	Histology
Eickhoff 1976			
Richie 1977	M50	Hematuria	Mucinous
Henry 1980	M58	Frequency	Mucinous
Bischoff 1980	F50	Incidental	Mucinous
Bartholomew 1984	M48	Pain Hematuria	Adenocarc.
Dalton 1987	F82	Recurr.Infect	Colonic A.C.
Chen 1991	F70	Hematuria	Mucinous
	F67	Hematuria	Mucinous
Ikeda 1995	M67	Dys/pollakis	Mucinous
Tripodi 1995	F81	Hematuria	Mucinous
Dahms 1997	F80	Hematuria	Mucinous

Another series was reported previously by Young et al. involving some patients of the same institute. It is not clear to what extent the patients had been already included in the previous report. In that series, however, only 5 were bilateral vs. 16 unilateral, with 4 at the left.
In a series of 16 adenocarcinomas, Conte et al. found ovarian metastases in 7/8 women, while Nitecki et al. reported to have observed ovarian metastases in 13 of the 23 women submitted to ovariectomy. In both series the side of the ovary was not given. Other reports are shown in table 9.34.

Another possibility is the presentation as a malignancy of the urinary bladder, after perforation through the wall. Some cases have been reported with an appendiceo-vesical fistula. The symptomatology is invariably hematuria with recurrent infection and an adenocarcinoma in the biopsy. CT is able to provide an effective differentiation of it from an urachal carcinoma. The reported cases of bladder invasion are summarized on table 9.35. Notice the slight (aged) fe-male preponderance of these patients.

Distant metastases subsequently occur in 20% of the patients and were mostly in the liver. Other localisations have been reported and were the first sign of an unknown tumor in the testis, ovary (review by Merino 1985), uterus, bone and other sites (see further).

Unusual Presentation

Several cases have been reported where the diagnosis of appendiceal adenocarcinoma was made during examination or laparotomy for a symptomatology, which turned out to be due to a metastasis. As well as the patients mentioned in table 9.35, DasGupta has also reported on three patients where the first presentation was an umbilical metastasis.

Table 9.36 - Adenocarcinoma of the Appendix
Presentations with Revealing Metastasis

Author	Patient	Site of Metastases
DasGupta 1966	M80	Several bone metastases
DasGupta 1966	M60	Pleural effusion
Edmondson 1967	M66	Paraplegia - bone metast.
Bodon 1967	M31	Ri.Epididymis
Otto 1970	F26	Bone and other metastases
Mehzad 1978	F50	Abdominal mass
Chang 1981	??	Peri-umbilical metastasis
Chang 1981	??	Supraclavicular node
Conte 1981	??	Supraclavicular node
Alenghal 1982	F78	Uterine bleeding
JavierGomez 1995	M51	Renal metastasis
Kobayashi 1997	F72	Pleural effusion

METASTASES from CANCER of the LARGE BOWEL

Although we are reluctant to include the cancers of the colon and the rectum in the same chapter, we were more or less obliged to do so, because the vast literature hardly makes any distinction between both as far as metastatic pattern and case reports are concerned. Prognosis and treatment are also not always discussed separately. The tumors at the various different colonic sites do not behave the same way as could be expected in view of the different embryological origin and anatomical situations.
We will try to separate the different sites as far as the literature reports make this possible.

Pathways of Spread

Rectocolic tumors are rarely localized and most will spread.
Local spread is initially intramural as discussed for esophagus and stomach, and is not uncommon. After perforation of the serosa, tumors can embolize in the veins in the direction of the general circulation and within the lymph channels towards the regional lymph nodes and further.
Invasion of neighbouring organs is not uncommon, but cannot be considered true metastasis. The ovaries, the pelvic muscles and the lumbar nerve plexus are often involved.
Venous spread along the portal vein is the main cause of liver metastases, but the perivertebral venous plexus (Batson) can be the source of other distant metastases.
Distant metastases are relatively rare, and not always correctly recognized.

Overall Metastatic Pattern - Autopsy Studies

Series reporting on overall metastases do not always make the distinction between the rectum and the colon, even between the different colonic sites. Data on the metastatic rate depending on the colonic site have not been reported.
Except for a number of sites, there is not much difference between the reported series, but this will depend on the autopsy protocol and the diligence of the pathologist performing the autopsy.
An apparently thorough study of 1541 patients was reported by Weiss et al. This study was solely of colonic cancers, although not explicitely stated.
They identified several groups

A. No liver metastases	869 (56.4%)
B. Only liver, no lung or other	420 (27.2%)
C. Both liver and lung, but no other	112 (7.2%)
D. Both liver and lung and others	140 (9.0%)

Only 22.5% of all patients had metastases in sites other than the lungs or liver (Table 9.37). The distribution within the four groups more or less confirms the cascade theory, which postulates that all metastases should follow the implantation of liver metastases. The path-way of the plexus of Batson is possible route that circumvents the liver. In another study of 163 rectocolic cancer patients, Patanaphan et al. found that 81 of 112 patients (72%) presented with liver metastases. In 33/51, the liver metastases were found during follow-up, resulting in overall 70% of the 163 patients.

Table 9.37 - Cancer of the Large Bowel
Non-hepatic and Non-pulmonary Distant Metastases
Autopsy Data on 347 patients (22.5% of 1541)
Data of Weiss et al. 1986

Abdomino Pelvic Sites	N	(%)	% of whole series
Abdominal Wall	12	(4%)	(°)
Adrenals	108	(31%)	7.0%
Gallbladder	14	(4%)	
Gut	37	(11%)	2.4%
Kidney	44	(13%)	2.8%
Pancreas	30	(9%)	1.9%
Porta Hepatis	5	(1%)	
Retroperitoneum	4	(1%)	
Spleen	52	(15%)	3.3%
Ureter-Bladder	14	(4%)	
Uterus	12	(4%)	1.6% of female
Extra Abdominal Sites			
Bone Marrow	93	(27%)	6.0%
Brain	38	(11%)	2.4%
Diaphragm	21	(6%)	
Esophagus	2	(0.6%)	
Leptomeninges	12	(4%)	
Mediastinum	4	(1%)	
Muscle (skeletal)	10	(3%)	
Myocardium	6	(2%)	
Pleura	43	(12%)	2.8%
Pituitary	1	(0.3%)	
Skin	17	(5%)	
Thyroid	13	(4%)	
Trachea	5	(1%)	

(°) when not given: less than 1%

In the same group there were only 18 or 11% lung metastases, 7% bone metastases and 2% brain metastases. Multiple sites were present in 10%.These figures confirm that recto-colon cancers remain within the abdomen, in fact within the pelvis and the liver.
Summarizing 15 published series on colon and/or rectum, Lee came up with the data on table 9.38.

Table 9.38 - Cancer of the Large Bowel
Distant Relapses in surgically treaten patients
Summarizing data of Lee 1998

Intra Abdominal		Extra Abdominal	
Liver (only)	54% (24%)	Lung (only)	27% (none)
Peritoneum	13%	Brain	3%
Lymph nodes (')	10%	Bone	5%
		Nodes	<1%

(') operated patients had lymphadenectomy

Liver is the most common site of distant metastases. From the data, the intrapelvic spread can not evaluated.
A specific study on rectal cancer was reported by

Slisow et al. (table 9.39). When the liver is involved as it is in a large number of cases, a high number of non-regional lymph nodes are observed.

Table 9.39 - Cancer of theRectum
Distant Metastases in Autopsy of 415 Patients
Data of Slisow et al. 1990

PelviAbdominal		ExtraAbdominal	
Liver	82.7%	Distant Nodes	58.3%
Peritoneum	16.1	Lungs	34.5
Adrenal	5.1	Bone	7.5
Ovaries (N=7)(')		Pleura	5.5
Pancreas	1.4	Brain	3.1
Spleen	1.2	Thyroid	1.7
		Skin	1.7
		Heart	1.2

(') Number of female patients was not given

These data do not differ very much from the data of Weiss for Colon NOS and confirms that rectal cancer is also a pelvic 'self-limiting' tumor.Reviewing the autopsies of 145 patients, Welch et al. came up with a number of interesting statements.

1. Right colon tumors had spread to local and distant sites in 90%;
2. Rectal tumors had spread locally in only 25%, to distant sites only in 25% and to both in 50%;
3. The liver was the most common site in both, followed by regional nodes and lungs;
4. Unilateral ureteral obstruction, an expression of local spread was seen in 25% of rectal tumors, 11% of sigmoid and in 14% of the right colon tumors. Bilateral obstruction was found in 21% of rectal cancers but not in the others;
5. The somewhat more frequent lung metastases in rectal cancers could almost always be explained by drainage from the hypogastric veins to the inferior vena cava;
6. Osseous metastases are more common in rectal cancers, probably explained by the paravertebral plexus of Batson.

Loco-Regional Spread

Rectocolon tumors first expand locally within the mucosa either longitudinally or circularly or both ways. Intramural spread has been consistenly demonstrated in rectal cancers. They then penetrate the different layers of the colonic wall through the serosa where they reach pericolic fat and loose tissue. They will either grow within the loose tissue or be picked up by lymph or penetrate veins, to be conveyed at distant sites, either to lymph nodes or capillary networks.

The efficiency of the spread will determine the involvement of regional lymph nodes and/or distant metastases, most frequently, as we have already seen, in the liver.

Lymph Node Metastases

The lymph nodes can be classified into four groups: the epicolic on the wall of the colon beneath the peritoneum, the paracolic medial to the wall at the mesocolic side, the intermediate and the nodes at the principal inferior mesenteric artery. The intermediate nodes follow the vessels in the mesocolon, the superior hemorrhoidal arteries for the upper rectum, the sigmoidal arteries and the left ascending colic artery and veins.The lymph drainage of the cecum and ascending colon follows the ileocolic vessels towards the root of the superior mesenteric artery and adjacent to the head and body of the pancreas.

Cells from transverse tumors follow the middle colic vessels in the transverse mesocolon joining the superior mesenteric vesels anterior to the head of the pancreas.The left colon drains its lymph along lymphatics within the mesocolon towards the root of the mesocolon. The principal nodes are the nodes at the inferior mesenteric artery. They are located at the root of the artery, where it originates within the aorta.

When involved, they can be seen slightly to the left of and anterior to the abdominal aorta and at the level of the third lumbar vertebrae (Granfield et al.).Tumor cells from the rectum can follow two ways:
- the superior hemorrhoidal route towards the mesorectum and mesocolon
- the lateral path along the middle and inferior hemorrhoidal vessels towards the hypogastric and obturator nodes and next to the para-aortic nodes. Detecting the nodes in the hypogastric group is not easy because several structures and vessels can displace or obscure them.

Beautiful studies have been done several years ago by Grinnel. We thought it worthwhile to reproduce a number of his very instructive drawings giving an excellent idea of the spread of the colonic cancers at various sites and of rectal cancers (fig.9.8).
Several authors have published data on the involvement of lymph nodes obtained by surgery for the different colon tumors. We extracted data from the article by Hida et al. (table 9.40 and 9.41).

Table 9.40 - Cancer of the Large Bowel
PeriColic Lymph node involvement (N=164)
Data of Hida et al.

	At tumor(')	Proxim.	Distal (°)
Right (N=36)	22%	33.3%	16.7%
Transverse(N=24)	33.3	0	12.5
Left (N=104)	63.5	20.2	11.5
pT1 (N=18)	11.1	5.6	0
pT2 (N=30)	43.3	6.7	3.3
pT3 (N=98)	67.3	22.4	14.3
pT4 (N=18)	83.3	44.4	33.3

(') nodes along tumor segment;
(°) nodes 5 cm from upper or distal margin

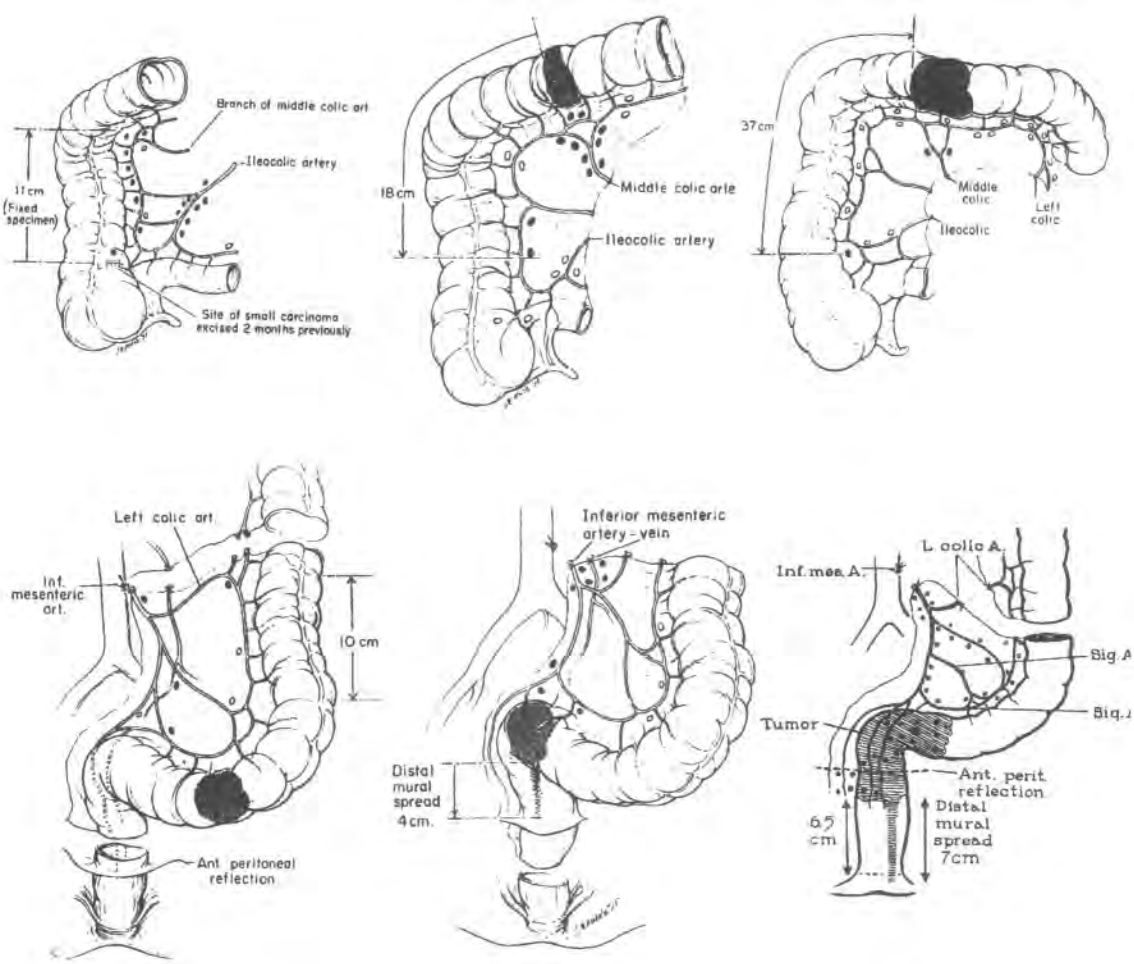


Fig. 9.8 - Typical pathology studies of resected colon or rectal cancers showing the mesocolic lymphatic involvement for the cecal, transverse, sigmoidal and rectal cancers. The lymphatic spread is clearly indicated and also the intramural spread of the rectal cancer. (From Grinell, with permission)

Table 9.41 - Cancer of the Large Bowel
Central Lymph node involvement (N=164)
Data of Hida et al.

	Central	Main(')	More
Right (N=36)	12%	6%	2%
Transverse (N=24)	0	1	0
Left (N=104)	32	12	5
pT1 (N=18)	0	0	0
pT2 (N=30)	6	0	0
pT3 (N=98)	30	15	5
pT4 (N=18)	8	4	2

(') lymph node more central than main lymph node

The data of Hida et al. clearly indicate a correlation between the site of the colon involved and the amount of positive nodes. Left sided colon cancers have a higher propensity for lymph node metastases. The pT status of the tumor parallels with a higher incidence of pericolic nodes but this also applies to central node involvement, with its limitation for radical surgery.

Pericolonic deposits, defined as discontinuous adenocarcinoma in fibro-adipose and desmoplastic tissues not associated with lymph nodes, have been described by a number of authors. Their prognostic value has been noted but not well appreciated until the recent work by Goldstein et al. It was observed in 89 patients or 21% of a group of 418 T3NOMO colon adenocarcinomas. While the absence of these deposits was associated with a drop by 12% in subsequent intra-abdominal metastases, the presence of even one deposit will lead to a doubling of the rate and when four deposits are found, this will amount to 70%. It seems that these deposits are a marker of a proportionnally higher incidence of intra-abdomial metastases relative to hepatic metastases.

Peritoneal invasion has hardly ever been studied. We found one study on 412 operated patients, of whom 242 or 58.7% had some peritoneal involvement confirmed at microscopy. Peritoneal involvement was defined either as tumor present at peritoneal surface or

tumor cells shown free in peritoneum and evidence of adjacent ulceration (Shepherd et al.). This is quite high for patients apparently previously treated by curative surgery. According to the site in the colon, it seems that cecal cancers have the highest incidence (table 9.42).

The instauration or at least attempts or even trials for aggressive treatments of peritoneal carcinomatosis has led to new insights in this dreadful and previously considered fatal clinical situation.

Other data have recently been provided by a multi-center study of Sadeghi et al. They collected 370 patients with a non-gynecological malignancy in the period 1995-1997 and reported many interesting demographic and anatomic data. In more than two-thirds digestive cancers were involved.

Table 9.42 - Cancer of the Large Bowel
Peritoneal involvement according to Site (N=412)
Data of Shepherd et al.

	N	N with	%
Cecum	75	53	70.6%
Ascend. - Hep.Flex	85	52	61.1
Transversum - Splen.Flex	69	42	60.8
Descending	23	10	43.4
Sigmoid	160	85	53.1

As far as colorectal cancers are concerned, peritoneal carcinomatosis (PC) was found in 118 cases, and a diagnosis of peritoneal metastases was made at first presentation in 58.4% of those. Overall, 66% of them were in PC stage III or IV. The mean age of the patients with PC was 62.3 yrs (range 20-92).

As mentioned previously, colonic cancers are the third most frequent source of the syndrome of pseudo-myxoma peritonei (PM). This rare phenomenon occurs in low-grade mucinous adenocarcinoma spreading all over the peritoneal surface. A series recently reported by Zoetmulder et al. mentions 24 cases with PM compared to 29 with true peritoneal metastases.

Non-Regional Lymph Node Metastases

Metastases in the non-regional lymph node such as the supraclavicular is not only unusual, but rare.
An extensive peritonsillar and cervical abcess containing streptococcus bovis was found to be a metastatic infection from an unknown colonic cancer (Goumas et al.).

Distant Metastases

The pattern of metastases is limited to a constant incidence of liver and lung metastases, whereas other sites have a low incidence, even to bone and to the brain. Except for liver metastases, the incidence of distant metastases is lower than for many other cancers.

Hepato-Biliary Metastases

Metastases to the liver are present in about 85% of the autopsied patients. They are even present in 50% of the patient at first diagnosis.
In spite of many hundreds of reports on the (palliative) treatment of liver metastases from rectocolic cancers, almost no pathological or anatomical data has been reported as far as site within the liver, multiplicity or amount of solitaries and correlation with the site of the primary is concerned. The different trial-coordinators should retrieve and report on their data.

To the extent that the data of Giacchi et al. permit conclusion, it would seem that the rate of liver metastases is somewhat higher in rectal and sigmoidal cancers (20 to 22%) than in other parts of the colon (16%).

The data of Holbrook et al. on the distribution of the metastases within the different segments of the liver were discussed in chapter 3. The data of Finlay et al. stress a higher incidence of occult ones (not detected before surgery) in segments VI and VII, together 74% of all 16 patients.

The influence of the histology type was studied by Rhomberg et al. In 90% of the liver metastases adenocarcinoma from 97 primaries was involved. There were 8 cases with mucinous adenocarcinoma of which 5 had liver metastases, but none of the 10 signet ring cell had liver metastases.

Okano et al. recently reported on 149 patients undergoing hepatectomy for metastatic rectocolon tumors. Although biased, there were 60 livers with a solitary tumor. Bile duct invasion was observed in 62 or 42%, of which 18 were macroscopic and 44 microscopically confirmed.

Finally, calcified liver metastases seem to be common. Hale et al. found that they were present in 11% of the patients with liver metastases at presentation. In a 4% more, calcified metastases developed during chemotherapy. They probably represented a kind of healing with calcium uptake within necrotic metastases.

Extrahepatic biliary obstruction with jaundice due to lymph nodes adjacent to the bile duct was reported in 8 cases by Warshaw et al. Primaries were at all sites along the colon from caecum to rectum. Ten years later, Sung et al. reported on 6 new cases from one institute, all caused by multiple periductal lymph nodes. They found 15 other cases in the literature. The interval from primary treatment to diagnosis of obstruction ranged from 0 to 108 months, with a median of about 1 year.
Obstruction was present at the hilum in 5 cases and duodenally in the three other cases.
Intrabiliary growth from hepatic metastases has been described in two series. Three cases were described by

Rullier et al. in male patients. Eight other cases were reported by Riopel et al. and four by Jinzaki et al. Most of the patients had intra-abdominal spread as well.
Five years after left hemicolectomy, one patient (F72) presented with jaundice and hepatomegaly. At surgery the whole duct lumen was found filled with a long papillary tumor; mucosal implant metastases (Dyess et al.).

Pulmonary and Bronchial Metastases

Parenchymal lung metastases are not as frequent as liver metastases. They amount to about 30% of cases still more occur during follow-up. In spite of many hundreds of reports on the surgical palliative treatment of lung metastases from rectocolic cancers, almost no pathological or anatomical data has been reported as far as site within the lungs, multiplicity or amount of solitaries and correlation with the site of the primary is concerned.
From a series of 159 patients who underwent surgical excision of lung metastases, 46% had originated from a rectal cancer. In 107, solitary metastases were present, what is understandable as they were selected for surgery. There were 20% with bilateral lesions and the others were equally divided over both lungs.
Of 185 patients treated, 30 or 16.2% developed pulmonary metastases. The lesion was solitary in only six (Schulten et al.).
Reporting a case metastatic to the H&N, Delfino et al. mention that the case was diagnosed after excision of two pulmonary coin lesions to have a cecal tumor.
A series of 18 patients with lung metastases submitted to surgery was reported on by Mouroux et al. The metastases was single in 14, twice multiple within one lobe, in one multiple within one lung and in one multiple in both lungs. The site was at the periphery in 15. The size varied between 1.5 to 6 cm with a mean of 3 cm.
We have no specific reports on metastatic pleuritis in colorectal cancers.

Compared with other cancers, reports on endobronchial and tracheal metastases are uncommon (table 9.43).
Carlin et al. reported on 9 cases and found 15 other cases in the literature (1969). Seven were female patients and 8 were from colon, while only one was from a rectal tumor. The literature review yielded 2 cecal tumors, 3 sigmoidal, 4 rectal and 6 colonic NOS. More recent reports are not available.
Radford et al. reported on the use of sputum cytology in patients with pulmonary metastases. From their data, it would appear that of the 22 patients they examined, 3 or 4 had endobronchial metastases.
A rare presentation of lymphangitic metastasis with bronchorrhea was reported by Shimura et al. in a 52 year old female patient, antedating the diagnosis of an ascending colon cancer. The lymphangitis was confirmed at autopsy.

Table 9.43 - Cancer of the Large Bowel
Tracheobronchial metastases
Literature Reports

Bronchi			Interval
Hermann 1982	M47	Rectum	4yrs
Berg 1984	M61	Rectosigmoid	3yrs
Casino 1992	M56	Descend.colon	42mo
Casino 1992	M68	Sigmoid	Reveal
Casino 1992	M57	Rectum	16mo
Lee 1997	M69	Rectum	1.5yrs
Tayama 1998	M51	Rectum	4yrs
Zias 1998	M75	Colon NOS	6 mo
Trachea			
Yeh 1965	F35	Colon Desc.	3 years
Conti 1994	M73	Sigmoid	1 year

Pleural metastases at autopsy number about 5%. They are apparently uncommon. Recently, Fernandez et al. reported on a man (M38) presenting with pleural effusion. CT showed subcarinal adenopathies and after some delay, a pleural biopsy disclosed mucus-secreting adenocarcinoma pointing towards a GIT malignancy. Barium enema showed a stenotic lesion at the hepatic flexure. There were no hepatic metastases.

Brain Metastases

According to the data of Weiss, 2 to 3% of the autopsied patients had brain metastases. However, several largely neurosurgical series have been reported. We have extracted the best data from the report of Hammoud et al. (table 9.44).
It concerned 100 patients of whom 24 were synchronous (type 2) metastases and 76 occurring during follow-up. More than half of the patients also had a large number of other metastatic sites. This was not a selected series as only 23 underwent surgery.

Table 9.44 - Cancer of the Large Bowel
Incidence of Brain Metastases
Data of Hammoud et al.

	N	With Brain Meta	
Cecum	1157	15	1.3%
Ascending	883	15	1.7
Transverse	300	1	<1
Descending	671	4	<1
Sigmoid	2100	23	1.1
Rectosigmoid	921	9	1.0
Rectum	2063	33	1.6
Single metastases		64	64% of all
Double lesions		11	
Multiple		25	
Supratentorial		48	48% of all
Infratentorial		33	
in both hemispheres		19	

The distribution according to the location of the metastases in the brain was given in the series of Ko et al. (table 9.45). The data are, however, not very accurate. Brain metastases developed in 40 patients, or

4%, of a series of colon cancer patients (Cascino et al.). One of them was a revealing metastasis (no details). The interval between discovery of colon tumor and the metastases ranged from 0-48 months, median 24.5 months.

Table 9.45 - Cancer of the Large Bowel
Location of Brain Metastases (N=53)
Data of Ko et al.

Temporo-Parieto-Occipital	37 - 62%
Cerebellum only	7 - 13%
Cerebellum and Cerebrum	7 - 13%
Frontal lobe	4 - 8%
Posterior fossa of Cerebrum	2 - 4%

In half of the patients, the metastases were multiple. Infratentorial metastasis was seen in 7 of the 20 single metastases. Only one patient had no other metastases. The left colon was the most frequent primary site (80%) but there were 75% left-sided primaries in the series overall.
In a recent series reported by Wronski et al. involving 73 patients who underwent surgical excision, 90% had solitary lesions and half were infratentorial. This was undoubtedly a biased series.

While the incidence is low, nevertheless several patients presenting first with signs of a cerebral metastasis have been reported. Details are shown on table 9.46. Striking is the fact that they are all derived from the French literature.
Apparently specific to brain metastases from colonic cancers is the presence of markedly hypointense areas on T2-W images, as Suzuki et al. have described on 6 patients and compared with images from other cancers.
Several other unusual cases have been reported as a meningitis carcinomatosa in two patients and an isolated dural metastasis from a sigmoid carcinoma.

Table 9.46 - Cancer of the Large Bowel
Type 1 (Revealing) Brain Metastases

Author	Pat	Site of Metast.	Primary
Ruelle 1987	F65	Parietal	RectoSigm
Hadjadj 1995	F57	Fronto-Pariet	Rectum
Alamovitch 1996	M68	Fronto-Pariet	Cecum
Gomez 1996	F48	Par-Occip.	Colon Desc.
Scotté 1997	M37	2x Cerebellum	Rectum
Brandicourt 1997	M64	Third Ventricle	Colon NOS
Garg 1999	M58	Left Cerebellum	Hepat.Flex.

Two weeks after right hemicolectomy, a M60 presented with acute bilateral ophthalmoplegia due to a cavernous sinus metastasis, more metastasis leading to death within a few months (Supler et al.).
Nguyen has reported on a patient (M75) presenting with hydrocephalus due to a cerebellar metastasis.
About one year after surgery, a patient (F51) presented with a solitary metastasis in the vermis, confirmed at craniotomy. Six months later she became quadriparetic because of a new metastasis within the cervical cord (Mirimanoff et al.).

Bone Metastases

Bone metastases are rare in recto-colonic tumors. In autopsy data, they account for 1 to 7%.
Of 5,352 cases registered between 1970 and 1995, 355 or 6.6% were identified as having bone metastases (Kanthan et al.).
The majority of the lesions were osteolytic, but other radiological patterns were also observed. It is noteworthy that 60 patients had no other metastases.

They are usually detected at plain radiology, CT or nuclea rscintigraphy, but TC99m CEA-scintography has been reported to detect metastases not seen in the other imaging methods (Bongers et al.).

Table 9.47 - Cancer of the Colon - Bone Metastases
Incidence according to Colonic Site

	Besbeas et al.		Katoh et al.	
	N	N with bone	N	N with bone
Cecum	62	1 (1.5%)	13	4 (30.8%)
Ascending	52	4 (7.6%)	16	3 (18.8%)
Transverse	30	--	11	2 (18.2%)
Descending	46	1 (2.1%)	5	1 (20.0%)
Sigmoid Colon	217	8 (3.6%)	35	6 (17.1%)
Rectum	347	25 (7.2%)	37	12 (32.4%)
Anus	11	--	--	--
All	765	39 (5.0%)	118	28 (23.7%)

The metastatic rate according to the site of the colonic tumor was extracted from the report of Besbeas et al. (table 9.47). Curiously, the ascending colon and the rectum have the highest rate.
The data of Katoh et al. are at variance and show a much higher incidence, overall 28/118 or 23.7%. The incidence is the highest for cecum and rectum cancers. The high rate in the ascending colon could well be due to cecal tumors. The skeletal site is reported by a few authors, but series are not large (table 9.48).

Table 9.48 - Cancer of the Large Bowel
Site of Bone Metastases

	Author	
Site	Talbot N=48	Katoh N=28
Skull	3	--
Cervical spine	1	2
Mandible	1	--
Clavicle	1	--
Sternum	--	5
Scapula	1	--
Humerus	5	--
Thoracic spine	8	17
Ribs	8	5
Lumbar Spine	30	21
Pelvis	11	2
Sacrum	3	4
Femur	4	5

The high rate of involvement of the pelvic bones and the lumbar spine can be explained at the hand of a segmental spread. They account for a large majority of

the metastatic sites. Metastases in the mandible are discussed further along with the head and neck metastases.
Revealing metastases (type 1) are relatively common and are mentioned in several small series (table 9.49).

Geh et al. recently reported on a series of 7 cases of sigmoidal cancers metastatic towards the cervical spine, of which 5 with spinal compression. In four patients, it was the first sign of metastatic spread, but in two there were no other metastases.
Several uncommon and sometimes revealing bone metastases have been reported, mainly acral ones (table 9.50). As usual, several cases are buried within small series, so that they are not retrieved if only the titles of case reports are taken in account. Remark that several cases are acral metastases and of the scapula. There is probably a serious amount of underreporting. The recto-sigmoid site is apparently preponderant.

Table 9.49 - Cancer of the Large Bowel
R evealing Bone Metastases
Data from small reported series(')

Author	Series	Pat	Site
Delannoy 1959	2/4 cases	M71	Rib - Colon Asc
		M55	Clavicula - Sigmoid
Louyot 1968	5/6 cases	F28	L3 -Rectosimoid
		M46	D12 - Rectosigmoid
		M59	Sacrum -Rectum
		M66	Pelvis - Rectosigm.
		M67	D4-D5-D10 Rectosigm
Seife 1973	3/8 cases	-M46	Pelvis - Rectosigm.
		F55	Scapula - Sigmoid
		M88	Sacrolliac - Desc.Colon
Solomon 1975	1 case	F38	L5(+extradural)+ skull
Cayla 1975	3/8 cases	F79	Femur - Cecum
		F58	D8-D9 - Colon Asc.
		F70	Spine- Sacrum -Sigmoid
Rodriguez 1992		M55	Sphenoid - Left Colon
Delva 1993 -	2/8 cases	M63	Spine - Sigmoid
		M67	Cerv.Spine - Sigmoid

(') see also following table.

A rare metastatic location is the coccyx. That it is very rarely reported may be due to the fact that axial radionuclide scan simply does not show the coccyx, as it is obscured by the active bladder. Bachmeyer et al. have demonstrated the necessity of a profile image in order to demonstrate a metastasis in the coccyx, while either CT or MRI fails to detect it.

Metastatic spinal cord compression was reported in a series of 39 patients with relatively advanced and widespread rectal or colonic cancers. The location were the same for both sites, except that there were more thoracal metastases for the colon and fewer for rectal tumors. The site was lumbar in 55%, thoracal in 32.5% and cervical in 12.5% (Brown et al.).
Five months after palliative resection of a cecal carcinoma, a patient (F59) presented with pelvic pain irradiating from a T12 vertebral lesion and epidural mass as demonstrated on MRI (Stübgen).
Some cases are included in the series involving spinal cord compression, but the high number in this report tends to make one to suspect a higher frequency than is generally believed.

Table 9.50 - Cancer of the Large Bowel -
Uncommon Bone Metastases

Author	Pat	Site	Interval
Rectum			
Sworn 1978	F79	Cuneif. Metatars	Reveal
Härkönen '80	F63	Ri.Great toe	Simult
Muller 1988	M77	Radius distal	3 years
Sanzari 1992	M41	Scapula (hyertroph)	6 mo
Sebag 1997	M48	Ossa Tarsi	4 years
Félizot 1999	M58	Talus Ri.	6 years
Tadross 2000	F74	Distal Tibia (")	16 yrs
Bachmeyer 2000	F55	Coccyx	4yrs(')
Sigmoid			
Seife 1973	F55	Scapula	Reveal
Seife 1973	F53	Foot (NOS)	2 years
Seife 1973	F64	Foot (NOS)	2 years
Seife 1973	M57	Big Toe	3 years
Cayla 1975	M77	Scapula	5 years
Hoehn 1979	F73	Os Pubis	Reveal
Hoehn 1979	F61	Skull - Ribs	Reveal
Husson 1986	M24	Os Iliopubis (hypertroph)	Rev'
Buckley 1987	F78	Os Trapezium	4 years
Sanzari 1992	M53	Scapula (hypertroph)	Reveal
Tuteja 1998	M48	Calcaneum	4 years
Transv.Colon			
Buckley 1987	F61	Prox phal. Ringfinger	2 years
Colon NOS			
Stuckey 1996	F76	Femur shaft (hypertroph)	4mo
Urvoy 1993	F71	Patella	10 mo
Schmidt 1994	F38	Calcaneum	5 years
Loevner 1997	M54	Occipital condyle	Reveal

(") patient had also a bladder carcinoma
(') see text ; (NOS):not otherwise specified

Bone marrow metastases, or at least malignant cells in bone marrow aspirates, have been found in quite a number of patients. As with other cancers, the data should theoretically show for distant spread, but there are more 'positive' patients than positive bone patients in the follow-up.
Of 156 patients, 42 or 27% presented with positive cells at the time of surgery (Schlimok et al.). Their influence on later metastatic incidence was not studied. Lindeman et al. found positive cells in 28 of 88 (32%) of patients with resected tumors. These patients had shorter survivals but no more bone metastases in the follow-up.
The combination of diffuse bone marrow invasion and bone metastases can produce the syndrome of leuko-erythroblastosis with anemia. Although not uncommon in breast cancer, it is very rare in recto-colon cancer. One patient (F49) was reported by Mathew et al., presenting one month after surgery for a rectal cancer with various complaints and an anemia of 8.7g/dL. She only had bone metastases, presumably originating from ewtension of the rectal tumor to the bone along Batson's plexus. This should explain the absence of other metastases in patients with bone metastases,

similar to what commonly happens in patients with prostatic cancer.

Head and Neck Metastases

In a literature review, Delfino et al. mention the retrieval of 8 cases of rectocolon tumors metastatic to the mandible, in the period from 1884 to1981.

Table 9.51 - Cancer of the Large Bowel
Head and Neck Metastases reported

Author	Patient	Site of Metastasis	Interval
Rectum			
Solomon '75	F38	Tongue	Simult
Moffat 1976	M56	Gingiva	Revealing
Meyers1977	F53	Parotid left	8 months
Schuchardt 1982	M59	Tongue Side	2years
Rentschler 1982	M73	Gingiva	3 months
Giles 1992	F55	Mandible Condyle	5years
Sadek 1983	F86	Meatus Acoustic	Revealing
Rusthoven 1984	F45	Gingiva	10 months
Tsianos 1985	M80	Gingiva	Revealing
Davidson 1989	M68	Tongue Side	3 years
Balestreri 1997	M57	Temp.Mandib.Jt.	2 years
Hilger 1998	F73	Larynx	3 years
Goldenberg 1999	M53	Tonsil Ri	2 years
Danikas 1999	F62	Os Malare	2 years
Bosca 2000	F48	Thyr. Cartilage	18 mo
Cecum			
Levy 1974	F80	Mandible	6 months
Delfino 1981	M65	Mandible	8 months
Mast 1987	F85	Gingiva	10 months
Ascending Colon			
Straith 1967	F60	Mandible	Revealing
Velez 1985	F66	Parotid Le	3 months
Cavicchi 1990	F59	Subglottic	1 year
Puxeddu 1997	M65	Larynx	2 years
Proximal Transversum			
Low 1994	M65	Tonsil Le	Revealing
Vasilevsky 1997	F81	Tonsil Le	Revealing
Sigmoid			
Lee 1974	M68	Nostril	4 years
Lee 1974	M59	Nostril	10 yrs
Naylor 1989	F65	Mandibula	Revealing
Rusthoven 1984	M65	Gingiva	8 months
Nicolai 1996	F53	Subglottis	4 years
Colon NOS			
Piatelli 1990	M54	Tongue Side	3 months
MacAfee 1993	M65	Temp.Mandib.Jnt	Revealing
Hall 1983	M60	Sphenoid -Sella	2 months

We show the several reported cases together in table 9.51. Of the 32 cases, 16 are female patients. This contrasts with the head and neck metastases reported in stomach and pancreas cancer, where the lar-ge majority are male patients. On the other hand, half of them were rectal cancers, concordant with the fact that about half of the rectocolon cancers are in fact rectal cancers. There seems not to be any favoured metastatic site except the mandible, with or without gingival involvement.

While several were revealing metastases, many other metastases appeared many years after surgery.

Metastases to the Spleen

According to the above-mentioned data of Weiss, metastases to the spleen were present in 15% of the autopsied patients.

Quite a number, 6 of 10, are female patients (table 9.52). It is evident that in all cases the primary colon tumor was at the left, except one from the cecum. There is a large time-interval, a mean of about 4 years. Another case was reported by Pieslor et al., but the metastasis was not a solitary one.

Table 9.52 - Cancer of the Large Bowel
Metastases to the Spleen
Literature Data

Author	Pat.	Primary	Interval
Dunbar 1969	M69	Rectum	6 years
Waller 1982	M72	Sigmoid	4 years
Slavin 1986	F81	Cecum	2.5 years
Cossa 1987	F56	Left Colon	2.5 years
Capizzi 1992	F51	Rectum	5 years
Thomas 1993	F72	Left Colon	11 years
Indudhara 1997	M74	Sigmoid	2 years
Mainprize 1997	F62	Splenic flexure	3.5 years
Weathers 1999	F33	Sigmoid	2 months
Achuthan 1999	M41	Rectum	1 year
Lee 2000	F66	Colon NOS	9 years

Worth mentioning is a prospective study of 25 left colon patients in whom splenectomy was performed (Konstadoulakis et al.). In none were splenic metastases found.

Metastases to the Male Gonads

Prostatic invasion from rectal cancer is not common, but is not to be considered as being true metastasis. A case of sigmoid colon that only metastasized to the prostate 16 months after resection was reported by Berman et al.

Up to 1998, 8 cases presenting with testicular metastases were reported (table 9.53). Meacham et al. reported on another with a intrascrotal metastatic tumor without invasion of the testicle. A similar case was reported by Bryan et al. Such cases must be differentiated from testicular and epididymal metastases.

All metastases in the scrotum were described as occurring at the right side, except one associated with a sigmoid cancer. Reviewing the literature in 1986, Jubelirer et al. retrieved 12 cases, of which 7 were at the right, 1 at the left and 3 bilateral. In one case, the side was not given in the report. The 4 cases of cecal tumors, for instance, had all scrotal metastases at the right, as well those reported later. This must undoub-

tedly be correlated with hemodynamic flow in reflux from the abdomen along the spermatic vein. A connection between the vena spermatica and the colonic veins has been demonstrated (see Chapter 4).

Table 9.53 - Cancer of the Large Bowel
Testicular - Scrotal Metastases Reported

Author	Pat	Metastasis	Primary	Interval
Moore 1982	M61	Ri testis	Cecum	Reveal.
Bensaude '83	M62	Ri testis	Rectum	5 years
Jubelirer 1986	M52	Le testis	Sigmoid	2years
Rasmussen '88	M53	Ri.testis	Cecum	Reveal
Meacham 1988	M32	Ri.scrotum	Colon NOS	Reveal
Bozza 1989	M77	Ri.testis	Rectum	3 mo.
Taviaux 1992	M58	Ri testis	Left Colon	Reveal
Bryan 1997	M75	Ri.scrotum	Sigmoid	Reveal
Lecae 1998	M50	Ri testis	Rect+Sigm.	Reveal

Table 9. 54 - Cancer of the Large Bowel
Metastasis to the Penis

Author	Pat	Primary	Interval
Whitelaw 1956	M62	Rectum	Reveal
Rees 1975	M41	Rectum	2 years
Rees 1975	M71	Rectum	2 years
Callen 1982	M62	Sigmoid	2 years
Bosch 1984	M64	Ri.Colon	2years
Bosch 1984	M62	Rectum	18 months
Khubchandani 1986	M71	Rectum	3 years
Doré 1989	M58	Rectum	Reveal.
Adjiman 1989	M71	Sigmoid	4 years
Hastier 1995	M77	Rectum	1.5 years
Lange 1997	M42	Sigmoid	2 months
Andresen 1997	M52	Left Colon	3 months
Perdomo 1998	M51	Cecum	Reveal
AlMashat 2000	M65	Rectum	19 months

Metastases to the epididymis have also been reported, one case at the right by Smallman (M60) revealing a sigmoid cancer and another by Kanno et al., a metastasis at the left 1.5 years after surgery for an advanced sigmoid colon. Reviewing the literature, they discussed intrascrotal metastases without differentiating testicular from intrascrotal or epididymal metastases.
One case (M56) with metastasis to the spermatic cord was reported occurring 6 months after surgery for a sigmoid cancer (Monn et al.).
Ramesh has reported on a cecal cancer presenting first with an epididymal metastasis (M70).

We found 11 reports on metastasis to the penis (table 9.54), but MacCrea et al. already retrieved 15 cases published between 1933 and 1957. There was only one from colon (NOS), and one from the anus, while all the other concerned rectal cancers.
In a literature survey spanning from 1870 to 1973, Rees found 19 cases of metastases to the penis from a rectal cancer. However, Haddad found in 1987, 45 cases. Sixty-five percent of the cases (20) in which the primary location was mentioned were from a rectal location. Penis involvement can be explained by retrograde venous or lymphatic flow, as surgery severely modifies the local hemodynamics.

Metastases to the Female Genitalia

A number of vaginal metastases have been reported.
In 1956, Whitelaw et al. reported on a vaginal metastasis revealing a sigmoid cancer. Another case was reported by Perrotin et al. in a women of 61yrs, also revealing a sigmoid cancer.
Four cases of true vaginal metastases were described by Raider in 1966. We are not aware of more recent reports. A few other particular cases are shown in table 9.55. The women reported by Zerner et al. had also bilateral ovarian metastases.
Much more frequent are metastases in the ovaries, probably because they are intrapelvic and relatively close to the colon. This topic has been much debated in the literature.

Table 9.55 - Cancer of the Large Bowel
Metastases to Female Genitalia

Author	Pat	Site	Primary	Interval
Whitelaw 1956	F52	Vagina	Sigmoid	Reveal
Lee 1974	F81	Vagina	Sigmoid	Synch
Lee 1974	F57	Vagina	Sigmoid	1.5 yrs
Zerner 1976	F54	Vagina	Cecum	Reveal
Goldstein 1981	F48	Uterus	Cecum	8mo
Bhirangi 1997	F86	Ri.Breast	Sigmoid	Reveal
Kobayashi 1999	F84	Clitoris	Rectum	Reveal
Nakagami 1999	F59	Cervix Ut	Rectum	6 mo
Walfisch 1999	F35	Myometrium	Sigmoid	5 mo
Chagpar 2001	F83	Vagina	Rectum	simult

Reporting on 148 women with colon cancer, Harcourt et al. found 8 patients at surgery with an ovarian metastasis or 5.6%. Blarney et al. reported 3.6% (36/998). The metastases were either from the cecum, the rectum or the sigmoid, being the closest site to the ovary. Sigmoid primaries seem however most frequent, pointing to some lymphatic or venous reflux.

In 1983, Herrera et al. reported on 10 cases where an unsuspected ovarian mass was found at surgery for a colonic cancer. Seven of the ten had bilateral involvement. They also reported on 30 patients who later developed later an ovarian metastatic mass. Twenty-five of the 40 tumors were left side tumors.
Surgery planned for an ovarian mass was found to involve ovarian metastases of colonic cancer in 17 patients.
Reviewing the literature up to 1983, Graffner et al. retrieved 75 reported cases (table 9.56). Remarkable is that about half of them should have originated from sigmoid primaries, but the side of the ovary involved could not be correlated. The anatomical 'nearness' is a most probable reason.

Reporting on 23 patients with large bowel cancer and ovarian metastases, Dionigi et al. mention one type 1-presentation, while in 16 the metastases was discovered at initial surgery. The total number of primaries was not cited. In 9 cases the primary was at the recto-sigmoid, 6 at the ascending and 5 at the descending.

Bilaterality, extrapelvic spreading, high mitotic index and a number of immunohistochemical tests favored the diagnosis of metastasis rather than of an ovarian primary.

Table 9.56 - Cancer of the Large Bowel
Ovarian Metastases (N=75)
Literature Review by Graffner et al.

Primary Colonic Site			
Cecum	1	Descending	6
Ascend.colon	6	Sigmoid	37 (49.3%)
Transverse	7	Rectum	18 (24.0%)

Literature data on the incidence of ovarian metastases cites figures of 2 to 13% (Birnkrant et al.). The same authors also found other interesting data relating to the menopausal status of the patient (table 9.57). The data are, however, perplexing as the rate is very variable.

Table 9.57 - Cancer of the Large Bowel
Ovarian Metastases dep. on menopausal status
Literature Review by Birnkrant et al.

Author	Patients		With Ovar.Meta	
	Pre M.	Post M.	Pre M.	Post M.
MacKeigan1979	24	138	25%	4.3%
Odariuk 1981	184	23	6.5%	21.8%
Blamey 1981	316	516	3.8	4.7
Cutait 1983	20	315	10.0	3.2

A series of 63 patients with metachronous ovarian cancer after recto-colon surgery was reported by Morrow et al. Half of the metastases were bilateral. A mean interval of 23 months, with a median of 12 months was found. They concluded that there is no clear correlation of the interval time with stage at surgery, but in about 40% the stage was not known! They did not correlate the interval time or the incidence of metastases with the colonic site.

It is a fact that the most common primary mimicking a secondary ovarian neoplasm, is adenocarcinoma of the large bowel. As discussed by pathologists, several were probably primary ovarian cancers of the endometrioid type (Lash et al.). Indeed, 19 of the 22 cases discussed were of the pseudo-endometrioid-mucinous type. Recognition of the characteristic features is important to avoid misdiagnosis and midirected treatments.

In spite of the relatively low incidence, prophylactic oophorectomy has been a matter of discussion. The age of the patients concerned, good oncological surgery and the prevention of late metastases with its serious morbidity, are serious arguments in favour of oophorectomy.
MacKeigan et al. reported on 162 women in whom they found 12 or 7.4% ovarian metastases. Four were at the rectum, 3 at the sigmoid, 4 at the cecum or ascending colon and one at the transversum.

A series of 255 patients was reported on by O'Brien et al. Of the 21 patients whose ovaries were apparently normal, none had involved ovaries. In 19 patients the ovary was adherent or macroscopically 'abnormal'. In 14 of them metastases were found. Of the 215 where no oophorectomy was performed, 8 later developed ovarian metastases.
Reporting on 41 patients with ovarian metastases from a colonic cancer, Lindner et al. mention that in 25 patients, or 61%, the diagnosis of a primary colonic tumor was made, while it was simultaneous in 13 or 32%. In three patients (7%) the ovarian tumor was found one to two months before the primary. The metastases were bilateral in 57% and originated from the rectum in 84% of the cases.

Metastasis to the breast from rectal cancer has been reported in a few cases (Lal et al.). Recently one patient (F42) was reported by Ozakyol et al. She presented with a breast nodule 6 months after hemicolectomy for a sigmoidal adenocarcinoma. There were, however, other abdominal metastases as well.

Metastases to Muscles

Several reports have appeared of patients with muscle metastases. Almost all were from the colon proper, as only two originated from the rectum. Striking is a large number of cases with gluteal muscle involvement, aside of the well-known propensity for the M.Iliopsoas (See Chapter 7), indicating segmental prevertebral nodal spread. Half of them were female patients and there were quite long intervals noted, as in fact none was a revealing metastasis (table 9.58).

One particular problem resulting of contiguous muscular invasion has been reported in some cases of cecal carcin-mas. An extensive local extra-mural outgrowth with inva-sion of the iliopsoas and down to the thigh associated with serious septic problems has been reported in a few cases (Bohrer et al.; Panwalker).

Non-Regional Lymph Node Metastases

Inguinal lymph node metastases are not uncommon in rectal cancer, especially in low-lying tumors. Of 3,215 patients with rectal cancer, 40 or 1.2% were found with biopsy-proven inguinal nodes. Most were T3-T4, but 10 were T1-T2 tumors located 2 to 4 cm from the anal margin.

We have reported on a patient treated for a sinusal carcinoma presenting with a right inguinal node, which was the first sign of cecal carcinoma.

Another study by Tocchi et al. observed 21 cases in a series of 863 or 2.4%, all being T3 tumors. In 16 of them the nodes were observed at follow-up.
Without mentioning the total number of patients treated, LunaPerez et al. reported on 18 with inguinal nodes at diagnosis. Extrapelvic metastases were obser-

ved in 14 of them. During follow-up, inguinal nodes were observed in 14, all treated with radical surgery. They occurred at a median of 26 months (range 12-53). All except one also had extrapelvic metastases.

Table 9.58 - Cancer of the Large Bowel
Muscle Metastases
Literature Survey

Rectum	Pat	Site of M	Interv
Caskey 1988	F30	M.Iliopsoas	6 months
Lampenfeld 1990	F75	M.Gluteus	2 years
Hashizume 1999	M59	M.Masseter	20 mo
Bosca 2000	F48	M.Obliq.Abdom.	25 mo
Sigmoid			
Belloir 1987	F76	M.Iliopsoas	8 years
Avery 1988	M67	M.Iliopsoas	4 years
Siddiqui 1998	F79	M.Adductores	1 year
Yoshikawa 1999	M54	M.Gluteus	2 years
Right Colon			
Stulc 1985	M74	M.Gluteus	2.5 years
Torosian 1987	F68	M.Biceps	2.5 years
Araki 1994	M66	M.Teres Major	3 mo
Homan 2000	F72	M.Adductor	12 mo
Transverse			
Laurence 1970	M51	Ri.Forearm	simultaneous
Caskey 1988	M62	M.Gluteus	6 mo
Cecum			
Laurence 1970	F70	Calf muscle	20 years
Colon NOS			
Caskey 1988	F71	M.Iliopsoas	no data
Glockner 2000	F44	Gluteal region	no data

Mediastinal nodes were detected in a patient (F57) 6 months after resection of ovarian metastases from a sigmoid cancer (Kuba et al.).
An axillary lymph node was mentioned in a case of widespread metastasizing right colon adenocarcinoma (Laurence et al.).
Reporting on 13 of 25 patients with liver metastases, Graham et al. showed at CT anterior diaphragmatic lymph nodes, as well as in 3 other patients without liver metastases (See Chapter 1). This demonstrates that the mediastinal and diaphragmatic nodes are probably much more frequently involved than generally believed. Their presence is undoubtedly indicative of poor prognosis and probably not worthwhile searching.

Gastro-Intestinal Metastases

A stomachal metastasis at the posterior wall of the upper part was disclosed after tarry stool passage in a M74, some time after surgery for a double (transverse and sigmoid) colon cancer. Was it a retroperitoneal node? (Hsu et al.).
Intestinal metastases are rarely encountered in colonic cancer. A duodenal obstruction was reported in a female patient of 81yrs, operated 5 years previously for a cecum tumor. Waxman et al. have reported on a man (M61) presenting eight months after colectomy with melena. At laparotomy, intramural and intramesenteric metastases were found at the mid-ileum, but no other intra-abdominal problem. Literature review at that time (1985) could only find 7 reported cases.
Green et al. found two gastric ulcers at endoscopy with thick rims at the greater curvature of the posterior wall at the junction of the fundus and the body, in a man (M56) two years after resection of the primary at the splenic flexure. We are not aware of other reports on stomachal metastasis from colonic carcinoma.

A solitary metastasis at the tail of the pancreas occurred 8 years after surgery of a rectal tumor in a 79yr old man. A series of 12 patients was studied by Charnsangavej et al. They stressed the difficulties involved in differentiating them from a primary pancreatic cancer, as CT-attenuation is similar. The presence of tumor necrosis or mucin can also be misleading. All cases involved tumors previously operated and located at the right side (cecum 3, ascendens 5 and transverse 4). The probable route to the pancreas is lymphatic. The total number of patients treated for right side colon is not mentioned, while they claim to have found 4 or 3% of pancreatic metastases in the 125 left-sided colon patients and another 4 with contiguous invasion.
Recently, a metastasis in the dorsal pancreas was described in a patient (F45) with pancreas divisum, three years after initial surgery (Pereira-Lima et al.).

Metastases to the anus have been described. While one can expect intra-mural spread for rectal cancer, it has been described in cases of sigmoid in two patients by Roullet-Audy et al. Another less clear case was published by Smiley et al.

Other Metastases

Ophthalmic metastases from colon cancer are rare. A patient with choroidal metastases (F48) was described by Cole et al. and another by Bastiaensen et al. Both had been operated on previously for a rectal cancer.

One patient (M37) presented with blurring of vision, narrowing of the visual field and headache. At MRI, a globular sellar lesion was found at histology to be a solitary metastasis of a sigmoid adenocarcinoma (Neroni et al.).

Skin metastases as well as Sister Joseph's nodule have been reported, even as first sign (Jager et al.). The metastases were at different sites within the abdomen, the thorax, the face and the scalp. One report concerned zosteriform metastases over the thigh and another over the axilla spreading to the ventral and back side (Ahmed et al.). Another patient (M75) was reported by Gmitter et al. with metastasis to the chin, associated with brain and lung metastases. Stavrianos et al. reported recently on a M78 presenting with a

cheek metastasis three months after surgery for a transverse colon cancer.
A multinodular eruption over the face and neck was the revealing symptom of a gastric cancer in a M52 (Sinicco et al.).
Recently, a patient (M63) was reported presenting with several cutaneous metastases on the trunk and the forearm. Their metastatic nature was disclosed at histology and a cancer at the descending colon found (Davis et al.).

Bahia et al. have reported on a F74 presenting one month after surgery for a right transversum colon cancer (Duke's C2T4) with crustous lesion of the scalp with several cervical lymph nodes, confirmed at histology as metastatic.

We found eight reports of thyroidal metastasis, all in female patients. Three were colonic NOS, one from the ascendens, one sigmoidal and three from the rectum. The interval time ranged from 2 to 4 years. Other metastases were present in three patients.
One patient (F69) was reported with thyroidal metastases, 8 years after surgery for sigmoidal cancer (Nachtigal et al.).
Cardiac metastases are rare. An intracardiac metastasis involving the right myocard and the pericard, presenting with tamponade one year after colon-surgery was reported by Steiner et al. A similar case was reported by Testempassi et al. Cardiac tamponade was the revealing situation of a colon tumor at the splenic flexure in a man of 46 (Kacenelenbogen et al.).
Right ventricular outflow tract due to right intraventricular metastases have been reported twice (Norell et al..; Birmingham et al.). In the latter case, it was the presenting situation, as the colon tumor was found only at autopsy.
The rare situation of a lung metastasis extending along the left pulmonary vein into the left atrium was reported recently in a man 8 years after surgery for a rectal tumor (Zissin et al.).

Colorectal cancers rarely metastasize to the kidneys. According to Issa et al., only 12 cases have been reported. All cases except their own one were asymptomatic. The metastases were large, solitary and exophytic.
Three years after surgery, a patient (M68) presented with persistent fever. Finally, nephrectomy was performed and disclosed a kidney in which the parenchyma had been entirely replaced by multiple metastatic tumor masses (Issa et al.).
Rioux-Leclercq et al. have reported on a M74 presenting with flank pain due to a 'silent' kidney, 16 years after surgery for rectal cancer. At pathology multiple pyelocaliceal metastases were found, a very rare type of renal metastasis.

Five years after sigmoidectomy, a patient (M60) died of severe liver metastases, obstructive ileus and an important left renal hydronephrosis. At histology, the pelvis of the kidney was found covered with several foci of adeno-carcinoma cells but without tumor tissue in the submucosa. This was interpreted as cell implantation from ureteral metastases (Shiraishi et al.).

Metastases in the adrenals are found in 5 to 10% of autopsied patients. In a series of 457 autopsies, Cedermark et al. disclosed adrenal metastases in 14%. Of these, 29, or about half, had bilateral involvement. They noted a higher incidence of this location when metastases were also present above the diaphragm.
An isolated right adrenal metastasis found at staging of a rectal carcinoma was reported by Bronstein. Three other cases found using CT because of raising CEA were reported by Watatani et al. Two had a rectal and one a sigmoidal carcinoma.
We are aware of two cases occurring during follow-up and presenting with an adrenal 'insufficiency' (Omoigui et al.; Black et al.). Another patient (F39) presented 8 years after surgery with a large solitary metastases in the left adrenal (Fujita et al.).

Metastases to the urinary bladder must be differentiated from contiguous invasion.
A vesical lesion was found subsequent to surgery in 4 patients reported on by Silver et al. with an interval of 9 to 66 months, but in one it concerned invasion by a recurrence of the vesical dome. Fitch has reported on a man (M49) where about 3 years after AP-resection a ureteral metastasis was disclosed at the middle third.

Ossifying soft tissue metastases have been reported in two cases. One was revealed by total body bone scintigraphy, with palpable lesions in the anterior abdominal wall (Stabler).

Causes of Death

As malignant rectocolonic tumors mostly spread within the abdominal cavity, the patient will progressively be undermined in some essential function of the different organs and in the nutrition of his body.

Table 9.59 - Cancer of the Large Bowel
Causes of death

Data of Taylor (1962)			
Local Progression			
with intestinal obstruction			36%
with kidney obstruction			25%
Intercurrent infection			33%
Metastases in lung			5%
Metastases in liver			25%
Data of Swinton et al. (1964)(N=320)			
Peritonitis	54 (17%)	Int.obstruction	20
Sepsis	39	Hemorrhage	18
Pneumonia	39	Operative	14
Pulm.Embolus	29	Liver failure	10
Cachexia	26	Various	66
Renal failure	21		

The more proximal tumors kill through hepatic failure

in 60%, frequently with concurrent pneumonia. Another third still succumb to local recurrence accompanied by ureteral obstruction, extensive invasion of the adjacent structures and present distant metastases.
Local disease primary or recurrent is the main cause - about 75% - of death in sigmoid and rectal cancers, with or without distant metastases. Liver and lung metastases or general cachexia is the cause in the other 25% (Welch et al.).
Other data have been provided by Taylor and by Swinton (table 9.59).

Overall Lesson

Rectocolon cancers are locally and regionally spreading tumors, remaining mostly within the abdominal cavity and spreading first towards the liver. Other distant metastases do not apparently follow any specific pattern and can be found in several unexpected locations even years after surgery in those patients surviving long enough to allow their development.

METASTASES from ANAL CARCINOMA

Spread

Lesions arising in the upper part frequently remain localized as an area of submucosal nodular infiltration. However, anal margin lesions tend to be circumferential.
Direct extension of proximal tumors tends to be upwards in the submucosa. Inferior spread seems to be limited by the suspensory ligaments which interdigitate in the region of the anal valves.
Tumors beneath the dentate line may even spread beyond the anus to the perianal skin. Lesions in the lower part tend to develop infiltrating ulcers. Like the middle lesions, they extend through the anal orifice but involve it only partly. Invasion of the sphincter and lower part of the rectum is frequent.
Anteriorly situated tumors may invade the rectovaginal and anovaginal septum in females, whereas in males the Denonvillers fascia provide a certain barrier against the penetration of the prostatic loge.
Extension to the vagina, bladder or prostate will occur in 15 to 20% of the patients (Dean et al.).
Laterally, the tumors can spread through the perianal muscles into the fatty intrapelvic tissue up to the bony pelvis (Cummings). Lateral growth into the ischiorectal fossa may present as an abcess or fistula, possibly with annular stenosis of the anus (Dean et al.).
The two areas of the anal zone both have different routes of lymphatic drainage. The neoplasms at or above the dentate line drain cephalad via the superior rectal lymphatics to the inferior mesenteric nodes and laterally along both the middle and inferior rectal vessels through the ischiorectal fossa to the internal iliac nodes (fig.9.9, 9.10).

Surgical series have identified pararectal lymph node involvement in 25% of the tumors of the proximal part (table 9.60). Involvement of the mesorectal nodes have been reported to increase depending on tumor size.

Table 9. 60 - Anal Cancer - Data on Metastases
Literature review Witzigman

6 series:69/512 (13.5%) Range 3.8 - 26.8%		
Pararectal nodes 25% of proximal tumors		
Mesorectal Size	<4 cm :	25%
	4-6 cm :	30%
	> 6 cm :	56%
Inguinal node anal tumor	:	10%
anal margin	:	25%
Distant metastases:	less than 10%	

Tumors at the anal margin/anal skin follow the lymphatics of the skin draining into the inguinal nodes (fig. 9.11 & 12). Neoplasms at the canal below the dentate line drain to the inguinal lymph nodes.

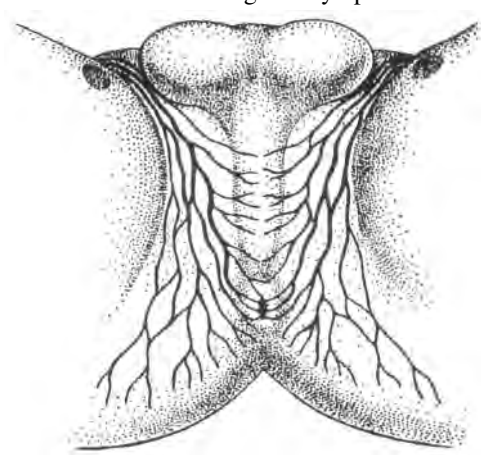


Fig. 9.9 - Lymph drainage from the anal margin and skin (Ackerman & Del Regato, with permission)

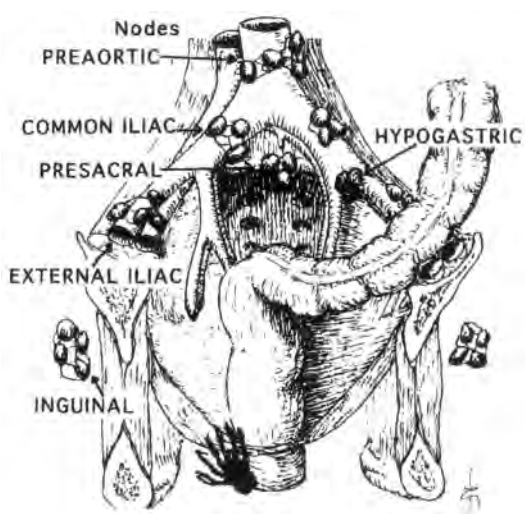


Fig. 9.10 - Intrapelvic Lymph drainage from the anal canal

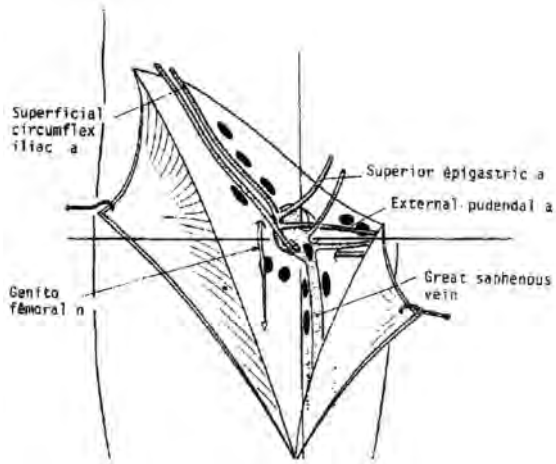


Fig. 9.11 - Schematic outline of the superficial and deep inguinal nodes. A transverse line at the level of the junction of the branches of the saphenous vein, separates the superior and inferior node groups (Scherrer et al., with permission)

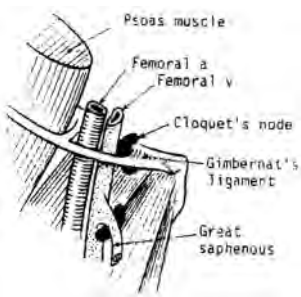


Fig. 9. 12 - Detail of the deep inguinal nodes (Scherrer et al., with permission)

If obstruction exists, lymph can drain to the superior rectal nodes or along the inferior rectal lymphatics to the ischiorectal fossa (Gordon).
A 59-year-old man was reported as presenting with a unilateral inguinal mass. Biopsy was immediately performed, disclosing well-differentiated squamous cell carcinoma. Finally, at examination a polypoid anorectal mass was found of the same histology. This should have been done before any other treatment (Gabiel et al.).

Using the clearing technique to examine surgical specimens from 26 patients, Wade et al. found only 34 positive metastatic nodes out of 305 nodes in the seven patients with positive nodes. They could not find arguments for an orderly lymphatic spread as many tumors had only pericolonic metastases without positive perirectal nodes. Data suggesting that lymph node metastases were most common in the perirectal region canot be accurate as 44% were found within nodes smaller than 0.5 cm in diameter (table 9.61).

Venous drainage through the superior hemorrhoidal plexus reaches the portal system, but the anal hemorrhoidal venous plexus represents a junctional area between the portal and the systemic venous system, so that metastases may reach the inferior vena cava through the iliac veins.

Table 9.61 - Anal Cancer
Frequency of pelvic node metastasis
Data of Mitchell (literature survey 1988)

	Mesenteric	Inguinal
Anal margin :	14.8%	39.9%
Anal canal :	16.4%	26.5%
Data of Scherrer et al., N=26,1990		
Tumor Size	<4cm	20%
	4-6cm	30%
	>6cm	50%
Site	Upper third	30%
	Middle third	25%
	Lower third	0-1%
Histology	Undifferent.	50%
	Interm.diff.	25%
	Well different.	10%

Distant Metastases

Overviews of distant metastases from anal cancer are absent in the literature, but the frequency seems low. They are reported in less than 10% of the patients at presentation and not much more during follow-up (table 9.62). They might however not be well documented. Anal cancer is a locoregional problem and seems to behave more like a skin carcinoma.
A recent survey on 81 patients by Faynsod et al. mentions 9 or 11% after a mean follow-up of 40 mo.

Table 9. 62 - Anal Cancer
Distant Metastases in follow-up

Site	Tanum N=106	Allal N=125	Jensen N=158	Wagner N=108
Liver	10	9	14	4
Lung	2	2	9	--
Skin	3	1	3	--
Bone	--	3	4	2
Brain	--	2	1	--
Peritoneum	--	--	3	--
Kidney	--	--	2	--
Heart	--	--	1	--
Para Aort.No	--	2	--	--
SupraclavNo	--	2	--	--
Dist.Ly Node	1	--	--	--

The typical metastases are in the liver and in the lung but have been described in the skin, bone, brain and the spinal cord.
Cases with multiple brain metastases (Garofalo et al.) subsequently followed by several others and of one single brain metastases (Davidson et al.) 8 years after first treatment have been reported.

It is worth mentioning is that 40% of the cancer deaths in the UKCCCR randomized trial (585 patients) were from disease identified outside the pelvis, but further details were not provided.
A patient with late (more than 5 years) metastases in the cauda equina was reported by Cho et al. Late dif-

fuse osteoblastic metastases were reported in a patient (F52) with an anal duct carcinoma (Krüger et al.). One patient with a thyroid metastasis was reported by Czech et al.
MacCrea et al. reported on a M43 presenting 10 months after abdominoperineal surgery for a squamous cell cancer of the anus, with a infiltrative metastatic lesion in the shaft of the penis.

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Caution: References are given for documentary purposes. Not all have been reviewed or used in the redaction of the text. We do not claim completeness of data. The references are as much as possible grouped per subject heading. For some headings, only reports after 1974 are listed.

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Cancer of the Anus

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10
METASTASES from CANCERS of the ABDOMINAL ORGANS

Hepatocellular Carcinoma
Cancer of the Gallbladder
Cancer of the Bile Duct
Cancer of the Pancreas
Islet-Cell Carcinomas
AdrenoCortical Carcinoma
Pheochromocytoma
Tumors of the Peritoneum

METASTASES of HEPATOCELLULAR CARCINOMA

Situated at the crossroads of several large vessels, hepatocellular carcinoma should result in a frequent dissemination of tumor cells. This, however, would appear not to be not true as at autopsy about half of the patients exhibit no distant metastases.

Spread - Metastases

The central position of the liver at the crossroads of large blood vessels must have a particular influence on the spread of hepatocellular carcinoma cells throughout the body. Nevertheless despite the likely predominance of this pathway of spread, other routes are also possible (table 10.1).

Table 10.1 -Hepatocellular Carcinoma
Spreading Pathways

1. Local expansion and invasion, with intrahepatic spread (daughter nodules)
2. Invasion of the vessels, particularly the vena portae and further also in the vena cava inferior, with trombi even up to within the right atrium
3. Spread along the ligamentum teres to the abdominal wall and muscles
4. The classical way of lymph nodes either downward to the hilus and retroperitoneal nodes, or through the diaphragm to the mediastinal nodes and further.
5. Intra-bile duct extension or invasion
6. Contiguous invasion in the neighbouring organs and structures, as colon, duodenum, gallbladder and stomach
7. Hematogenous spread all over the whole body.
8. Seeding through biopsy site

Two other aspects distinguish hepatocellular carcinoma from other tumors.

1. A relatively high proportion of the metastases present before the diagnosis of the primary is made. In other words, compared with other primary tumors, HCC frequently presents with its metastases first.
2. Quite a number of these metastases either in the brain, the oral cavity, the thorax or in the abdomen reveal themselves through spontaneous and profuse acute bleeding, due to their hypervascularity.

Autopsy Data

An autopsy study by Nakashima et al. identified three different patterns (table 10.2)

Table 10..2 - Hepatocellular Carcinoma
Distant metastases: Autopsy study by Nakashima

Hematogenous		Lymphogenous		Local Invasion	
	87.5%(')		41.7%(')		34%(')
Lungs	51.6%	liver hile	14.7%	to diaphr.	10.6%
Adrenal	8.4%	at pancreas	10.7%	gallbladd	5.8%
Bone	5.8%	at aorta	8.0%	stom-intest	5.8%
Pancreas	3.1%	at stomach	5.3%	periton.	5.8%
Heart	0.8%	Mediast.	5.0%	brain/men.	3/37

('): % of the metastases, other percentages relate to the whole group of patients

In 1981, Lo et al. reported on autopsies performed on 287 patients with HCC. They compared the incidence of metastases in cirrhotic and non-cirrhotic patients. Remarkable is that there were proportionally more metastases in the non-cirrhotic group, both overall as well as for the five most frequent sites (table 10.3).

Table 10. 3 - Hepatocellular Carcinoma
Frequency of metastases at autopsy
Data of Lo et al.,1981

	Cirrhotic	Non-Cirrhotic
N with metastasis	137/225 (60.8%)	45/62 (72.5%)
Lung	32.8%	40.3%
Ly nodes at hilus	14.2	22.5
Ly nodes elsewhere	8.8	16.1
Adrenals	6.6	9.6
Bone	2.2	11.3

Other reported series are shown in table 10.4.
It could be that patients with cirrhosis die earlier due to their evolutive liver disease and before metastasis could establish. Most patients indeed presently succumb rather to their liver pathology and its compli-

cation than of the metastases. Of 173 patients surgically treated by any means except transplantation and with a minimum follow-up of 3 years, only six developed distant metastases: 3 in bone (femur, pelvis, sternum), 2 in the lungs and one in the adrenal (Inagaki et al.).

Table 10. 4 - Hepatocellular Carcinoma
Incidence of distant metastases - literature series

	Patton(*) 1964 N = 60	Eldomeiri (°) 1971 N = 137	Orcel 1971 N = 105	V.Gossum 1985 (+) N = 126
Lung	70%	34/137	25%	24/126
Lymph N.	45%	--	--	38/126
Adrenal	13%	--	7%	5
Spleen	2%	--	--	--
Bone	13%	14	1%	12
Peritoneum	4%	--	--	8
Kidneys	4%	--	--	--
Brain	--	4	--	--
Heart	2%	--	--	--
None	4/60	--	--	--

(*)Autopsies (°)Clinical 31% of the patients had metastases. 10% had regional metastases.

Pleura	13
Skin	4
Pancreas	2
Thyroid	1
Brain	1
Esophagus	1
97 Ca/21 Chol.	----------
8 other carc.	
Tromb. v.portae	44
v.cava	15

Reviews by Lee et al. (1987) and the autopsy data from Kaczynski et al.(1995) yield in fact the same distributions. Unfortunatedly, they did not correlate the results with the tumor site, size and histological aspects of the primary tumors.

Distant metastases were observed in 145 or 67.1% of the 216 HCC patients who came to autopsy, as reported by Polterauer et al. (table 10.5).

Table 10.5. -Hepatocellular Carcinoma
Distant Metastases at Autopsy (N=145)
Data of Polterauer et al.

Site			
Vessels	70.3%	Pleura	13.8%
Lymph Nodes	31.7	Peritoneum	9.7
Lung	26.2	Adrenal	9.0
Liver	19.3	Diaphragm	6.2
Bone	16.6	Kidney	4.8

From the data of Peters and of Ho et al, Lee et al. remarked that there were proportionally fewer distant metastases in cirrhotic patients: 40 to 50% vs 30% in non-cirrhotic. A metabolic influence could, however, also be responsible, in view of the fact (as mentioned in Chapter 3, that there are fewer liver metastases in cirrhotic patients.

Apart from the classicaly metastatic sites, San Jose reported in a small number of their 80 patients metastases in the small bowel, the spinal cord, the thyroid, the stomach and the diaphragm.

Recently, a clinical series was reported on by Katyal et al. They reviewed the records of 403 consecutive HCCpatients who underwent CT and were treated at their institute (table 10.6). Extrahepatic metastases were identified in 148, or 37%. In 15, the disease was widespread and diffuse.

Table 10. 6 - Hepatocellular Carcinoma
Site of Distant Metastases Clinical and CT-study
(N=148) Data of Katyal et al. 2000

	Incidence	With other(')
Supra-Diaphragmatic		
Lungs	55%	28%(")
Brain	2%	all
Esophagus	1%	1/1
Diaphragm	1%	2/2
Infra-Diaphragmatic		
Adrenal	11%	44%
Peritoneum-Omentum	11%	56
Duodenum	1%	1/1
Pancreas	1%	1/1
Bladder	1%	1/1
Seminal vesicle	1%	1/1
Other		
Lymph nodes (°)	53%	72%
Regional	41%	68
Distant	12%	83
Musculoskeletal	28%	66

(') at initial presentation
(") of the patients with metastasis at that site
(°) detailed further in table 10. 11

Distant metastases are apparently confined to lungs, lymph nodes, the peritoneum and the musculoskeletal system.

Intra-Hepatic Spread

Local expansion and invasion with intra-hepatic spread occurs when the malignant cancer clones, expands and grows, displacing normal liver tissue. The tumor (or the host) apparently forms a capsule, delimiting the tumor from environment.

As a rule, the invasive spread proceeds along intra-trabecular pathways, remaining within their allotted space. Destroyed hepatocytes are replaced, the tumor cells then dilate their locality and usually distend and rupture the network of reticulin fibers. This signifies that HCC is rather poor on fibers, an interesting criterium by which to identify small minimal cancer foci.

However, in many instances, the malignant cells will seek further expansion and will invade normal liver tissue and eventually the vessels.

Work done by Toyosaka et al. shows that tumor spread

starts with intracapsular invasion, progresses to extracapsular invasion, intravascular spread and finally to intrahepatic metastases (fig. 10.1).

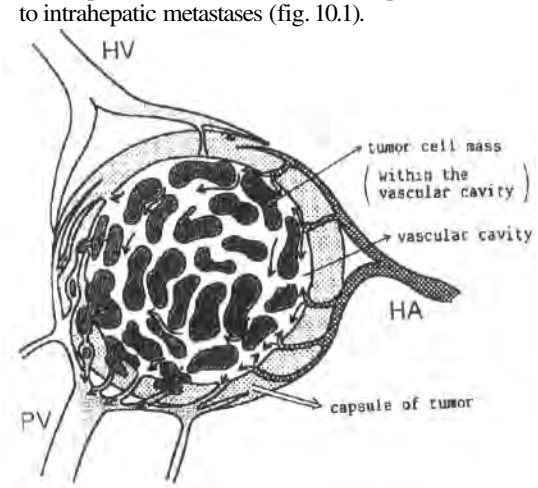

Fig.10.1 - Vascularisation of a hepatic tumor. HA: hepatic artery or feeding artery; PV: portal vein serving mainly as efferent vein; HV: hepatic vein (from Toyosaka, with permission).

Autopsy studies revealed that many satellite or daughter-nodules can be found around a primary, and may even have eluded detection by the imaging studies. There has been ample discussion in the literature about the nature of these nodules. Are they really metastatic or daughter nodules, or synchrone or metachrone new primaries?

This has recently been addressed by researchers particularly by Toyosaka et al., in a well done pathology-study. Their results support the fact that the nodules are intra-hepatic metastases. The arguments are:
- in all resected specimens even with multiple tumors, a definite primary can be recognized;
- the daughter nodules are mostly found in the same or adjacent portal branch area;
- macroscopic thrombi are present in 16.5% of the patients but in the hepatic vein only in 2.2%.

This has also been examined with US-graphy by Someda et al. They examined how the arterial dynamics in the hepatic artery supplying normal or tumorous tissue were modified. The pulsatility index and the systolic velocity of the hepatic artery supplying a tumor was changed significantly when the tumor attained a volume of 3cm and correlated with tumor size. This corroborates with the fact that the neovascular vessels have very thin walls, a scanty smooth muscle layer and few elastic fibers compared with normal arteries. Such a vascular bed must have a higher distensibility and decreased impedance.

One particular landmark in the evolution of a liver tumor is the formation of a capsule. According to Sasaki et al., capsule formation results from the compression of the surrounding parenchymal tissue during the process of expansive growth of the tumor.

The capsules are either distinct, fibrous, hyalinized and several millimeters thick, or thinner pseudocapsules composed of compressed reticulin stroma The incidence of encapsulation varies widely ranging from 4 to 85% and is common in Asian patients and in cirrhotic Europeans.

The prognostic significance of capsule formation is disputed, but several reports mention lower tumor invasiveness, lower incidence of venous permeation and liver invasion, a higher incidence of negative section margins, better survival and less likelihood of recurrence (Ng).

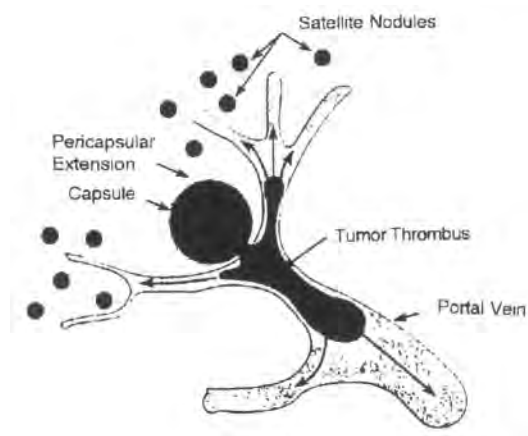

Fig.10.2 - The transcapsular and portal extension of HCC (modified from Farges et al., with permission)

Invasion of the vessels, occurs particularly in the vena portae and further into the vena cava inferior, with trombi even up to within the right atrium (fig. 10.2).

The same work by Toyosaka clearly showed that the 'efferent' vessel of a HCC tumor is the portal vein. The pressure in this vessel is lower than in the hepatic vein or artery. This is in fact a retrograde way, the portal circulation going normally the other way. This is even more marked in cirrhotic livers, because of impaired drainage by the hepatic vein.

Of 225 cases, 64.7% had invasion of the portal vein, 23.3 % in the hepatic vein, of whom almost 90% had portal thrombus as well. Of the 47 with the portal thrombus, 23% had a thrombus up to the right atrium (Nakashima et al.).

According to Ohwada et al. reporting data from a Japanese survey, the incidence at autopsy of tumor extension to portal vein and inferior caval vein is resp. 62.2% and 12.5%. At surgery, this amounts 15.5% and 4.8%. Tumor thrombi extending to the right atrium occurred only in 0.67 to 1.5% of primary tumors.

HCC thrombi in the portal vein can be either actively growing or necrotic. If growing, they receive even arterial supply within the thrombus with hepatofugal blood flow in the portal vein.

Unlike them, hepatic vein thrombi grow actively and at a faster pace. More than 50% of all HCC have portal vein invasion and 20% of the hepatic vein (Okuda).

As portal vein invasion is an important prognostic factor, Adachi et al. tried to identify risk factors for the portal invasion. In an univariate analysis on 252 patients, they cwere able to correlate it significantly with seve-ral factors, but in multivariate analysis only to three factors, viz. tumor size, histology grade and capsule formation (table10.7).

Table 10. 7 - Hepatocellular Carcinoma
Risk Factors for portal venous invasion
Data of Adachi et al. ,1996

In Univariate analysis	In Multivariate analysis
Tumor Size > 3cm (')	Tumor Size >3cm (')
High Grade (3 or 4) (')	High Grade (3 or 4) (')
Presence of fibr.Capsule (')	Pres. of fibr.Caps. (*)
Mitotic rate > 4/10 HPF (')	--
Peliotic changes (')	--
Tumor necrosis (')	--
Giant cells	--
High platelet count (P=0.0017)	--
Low level ICG-R15(°)(P=0.0029)	--
No Cirrhosis (P=0.0211)	--

(')= P<0.0001. (*)P=0.0204.
(°) Indocyanine-Green Retention test

Intra-atrial growth was examined in 18 patients by Kojiro et al, in a series of 439 HCC autopsies (4%). The tumor thrombus extended from the hepatic vein over the inferior cava to within the atrium, and in five cases the thrombus had extended within the right ventricle. The clinical manifestations are a diuretic-resistent edema of the lower extremities or marked venous dilatation over the abdominal wall. Tachycardia can be present.
The patient can succumb quickly to cardiac failure, tricuspid valve insufficiency and pulmonary thromboembolism.

Table 10. 8 - Hepatocellular Carcinoma
Tumor Pressure and its correlation with survival
Data of Tanaka et al.

	Portal invasion and/or intrahepatic metastases	No Portal Invasion and/or no intrahepatic metastases
	N= 22	N= 8
Pressure (cmH20)	14 ± 3	4 ± 5
Positive Gradient(')	82%	14%
Survival 5 yrs.	19%	73%

(')Positive gradient means a higher pressure within tumor than in portal vein.

Investigating physical factors determining tumor spread from a HCC, Tanaka et al. examined intratumoral pressure in 70 patients. Tumor pressure is significantly higher in the encapsulated form and non-necrotic tumors. It increases with worsening chronic liver disease, and non-significantly with tumor size. The differentiation correlates with tumor pressure to the extent that in moderately differentiated tumor, there was generally a well-preserved capsule. The higher the pressure, the higher the risk in spread as is seen in the survival of the different groups (table 10.8).

Spread along the ligamentum teres hepatis to within the abdominal wall and muscles is insidious.

> Ligamentum teres is a fibrous remnant of the fetal umbilical vein, extending from the umbilicus to the left lobe of the liver. Within the free margin of the falciform ligament it extends from the umbilicus in a cephalad, right-ward course up to the umbilical portion of the portal vein. It seems, however, that the lumen not always completely obturates but without an opening to the portal vein. The opening however can be 'restored' in situations of portal hypertension, providing an emer-gency and well-known shunt for diagnostic and therapeutic procedures. Corrosion anatomic studies have also showed the possibility of adequate communication.

As hepatocellular carcinoma frequently invades the portal vein, it must be possible for a tumor within the left lobe to spread along the ligamentum towards the umbilicus and the abdominal wall. A patient presenting with abdominal wall mass in whom then a tumor of the left liver lobe was diagnosed has been reported by Kim et al. Only one case of umbilical metastases has been reported, to our knowledge (Raoul et al.).

Lymph Node Metastases

Lymphatic spread occurs either downwards to the hilus and retroperitoneal nodes, or through the diaphragm to the mediastinal nodes and further.
Hepatic lymphatics can be divided structurally into capsular and intrahepatic lymphatics (Magari, cited by Toyoda, 1996). Much of the capsular lymphatics run towards the hepatic hilum and drain mainly into the celiac system. However, some capsular lymphatics on the superior surface run towards the right and left triangular ligaments and must communicate with the diaphragmatic lymphatics.

Intra-hepatic lymphatics have two drainage systems:
- the periportal and ductal system and
- the perihepatic vein system.

Most hepatic lymphatics belong to the periportal and ductal system, emerging at the hilus and draining into the coeliac nodes. The remainder belong to the perihepatic vein system and drain mainly through the lymphatics accompanying the hepatic veins. The perihepatic vein lymphatics flow into the thoracic cavity (Toyoda). From the celiac nodes, they drain to the thoracic duct and peritoneal spread is more frequent than not.
According to Williams et al., cited by Araki et al., 1988, the liver lymphatics are to be divided into a superficial and a deep system.

The superficial system drains in 4 directions:
- along the vena cava inferior to nodes around its terminal part;

- converging along porta hepatis into the hepatic lymph nodes;
- perforating the diaphragm around the esophagus towards the pericardial nodes;
- along the art.phrenica inferior across the right crus of the diaphragm into the celiac nodes.

The deeper system divides into two routes

- one along the hepatic veins and accompanying the vena cava through the diaphragm and ending around the vein;
- descending from the the porta hepatis to end in the hepatic nodes, in fact called the portal nodes.

More practical is a division in two parts: an upper connecting system draining to the mediastinum, and a lower part to the abdominal cavity (fig. 10.3).

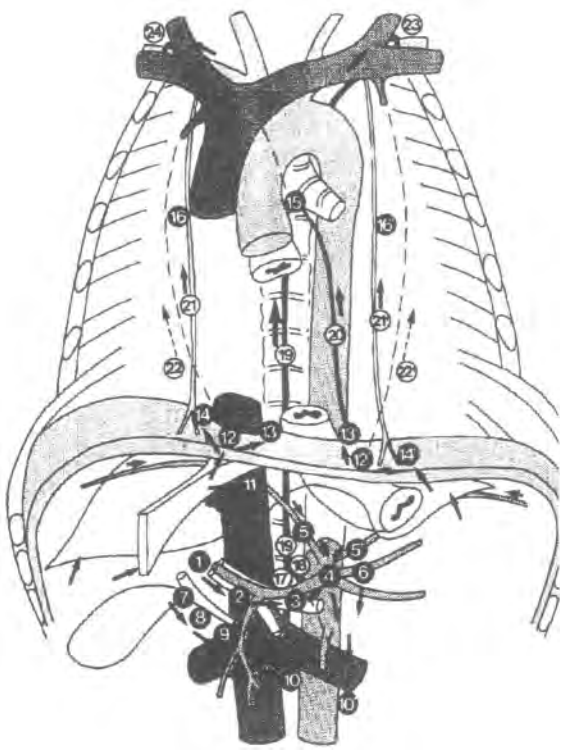

Fig.10.3 - Lymphatics from the liver:
Lymph Nodes (1) hepatici; 2/3 along art.hepatica prop.comm.; (4) coeliaci, (5) along art.phrenica; (6) art.gastr.sinistra; (7) bile duct (8) foraminalis; (9) pancreatici super.; (10) aortici later.; (11) praecavales (12) praepericardiales; (13) juxta-oesophage-ales; (14) phrenici super.; (15) tracheobronch.; (16) mediastin.ant.; Lymph vessels:(17) truncus lumbalis dexter; (18) tr.lumbalis sinister; (19) ductus thoracicus; (20) post.mediast. chain; (21) ant. mediast.chain (22) along thorac.vessels; (23) left venous angle (24) right venous angle (From Trutmann et al., with permission)

As could be expected, accurate data on lymph node metastases in living patients are not available. In the autopsy series of San José, 21% had lymph node metastases including mediastinal ones. Of these, 15 pa-tients had no other metastases. Araki et al. could detect abdominal lymph nodes by CT only in 5 out of 79 (6.3%) consecutive patients. Almost all these patients had tumors larger than 5 cm. The data contrast with their own autopsy data where they found positive lymph nodes in 35% of the patients (table 10.9). The data are compared with those of Nakashima.

From the above description, hepatic tumors located immediately under the diaphragm can spread to glands in the mediastinum, the thoracic duct and further to the supraclavicular nodes or Virchow-Troisier node. This node can be the presenting sign of many infra-diaphragmatic tumors, hepatocellular carcinoma inclusive (Kew). Its incidence is probably underreported.

Table 10.9 - Hepatocellular Carcinoma
Lymph node metastasis - Autopsy data

	Nakashima 1983 N=225	Akari 1985 N=482	Watanabe 1994 N=660
Overall positivity	26.7%	35%	25%
Abdominal			
Hepatic hilar node	14.7%	20.5%	
Para-pancreatic	10.7	9.9	
Retroperitoneal	5.8	9.7	
Peri-stomachal	5.3	4.3	
Mesenteric	ng	1.4	
Para-aortic	8.0	7.4	
Thoracal			
Pulmonary hilus	ng	7.4	
Peri-bronchial	ng	7.6	
Mediastinal	4.9	ng	
Para-tracheal	4.9	ng	
Peri-carinal	4..0	ng	
Supraclavicula	2.2	ng	
Neck	3.1	ng	

At autopsy of 660 patients dying of HCC, Watanabe et al. found 168 patients with any lymph node metastases, or 25%. The incidence according to tumor size increased from 19% with tumors smaller than 6 cm to 48% in tumors larger than 15cm.

Table 10.10 - Hepatocellular Carcinoma
Lymph node metastasis - Autopsy data
Data of Watanabe at Autopsy

Site	Right U. N=71	Right L.	Left	Overall N=660
Abdominal				
Hepatic hilar	57.1%	58.3%	58.3%	13.5
Para-pancreatic	62.9	50.0	54.2	13.6
Retroperitoneal	14.3	16.7	29.2	4.2
Splenic hilar	11.4	8.3	16.7	2.1
Peri-stomachal	11.4	8.3	45.8	10.8
Para-aortic	54.3	66.7	33.3	10.5
Thoracal				
Pulmonary hilus) Peri-bronchial)	31.4	25.0	20.8	7.1
Mediastinal	25.7	8.3	12.5	3.8
Para-tracheal) Peri-carinal)	31.4	25.0	16.7	7.7
Supraclavicular	5.7	0	8.3	1.8
Neck	11.4	0	12.5	1.8

Lymph node metastases at the hilar port and peri-pancreatic site are the most frequent. They are most

pancreatic site are the most frequent. They are most frequent for tumors in the left lobe at the perigastric and retroperitoneal sites (table 10.10). Two cases have been reported where a superior mediastinal syndrome were the presenting clinical situation of unknown HCC. Both were male patients (Kew,1989).

Clinical data were recently published by Katyal et al. Apart from distant metastases (see table 10.6), they detailed the involved metastatic lymph node groups (table 10.11). The high number at the cardio-phrenic site should be noticed.

Table 10.11 - Hepatocellular Carcinoma
Clinical and CT Lymphatic Dissemination (N=148)
Data of Katyal et al., 2000

Regional Group (41%)		Distant Groups (12%)	
Periceliac	33%	Mediastinum	39%
Porto-hepatic	23	Pretracheal	17
Para-Aortic	15	Paratracheal	1
Portocaval	10	Aortopulmonary	1
Peripancreatic	7	Prevascular	1
Aorto-Caval	7	Precarinal	1
Retrocaval	5	Cardiophrenic	28
		Mesenteric	1
		Internal Mammary	1
		Perirectal	1
		Retrocrural	1
		Iliac	1
		Paraspinal	1

Spread to the supraclavicular nodes can have two causes. Firstly, there may be direct extension along the lower end of the internal jugular lymph trunk, draining into the thoracic duct just before the latter enters the junction of the left subclavian and internal jugular vein and where the upper end of the thoracic duct is itself invaded. Furthermore, malignant cells will gain access to the node by refluxing up the lumen of the internal jugular lymphatic duct and the efferent duct of the node, following pressure changes in the thoracic duct by respiratory efforts or occlusion of the thoracic duct into the venous system by tumor cells (Kew, 1989).

A very rare presentation of diffuse (lymphoma-like) systemic lymph node metastases has been described by Toyada et al. concerned a small tumor of 18 mm in the right lobe.
A combined presentation with supraclavicular and mediastinal metastatic nodes, associated with a superior vena cava syndrome in a M67 led to the diagnosis of a HCC (Lau et al.).

Intra-Abdominal Spread

Bulky intraabdominal or intrapelvic extrahepatic masses can sometimes not be differentiated at imaging from another primary, as has been pointed out by Longmaid et al. They reported on seven patients with large metastatic masses in the pancreas, the retrogastric and even in the adrenal, which all where found to be metastatic masses from a 'small HCC'.

Invasion of Contiguous Organs

Contiguous invasion in the neighboring organs occurs when the hepatic tumor is located at the periphery of the liver. Tung et al. documented 21 patients (14% of all their patients undergoing resection) in whom 'en bloc' resection together with the invaded structure, was necessary: it concerned the diaphragm in 16 patients, the colon in 2, the right adrenal in 2, the abdominal wall in 2 and the great omentum in 1. Histologic confirmation of the invasion was only obtained in half of the patients.
Wu et al. have reported on 24 patients subjected to an 'en bloc' resection, but invasion was also only confirmed in 13, of whom 5/14 in the diaphragm and one in the gallbladder. The mean survival of the patients was only 15.3 months, compared with 40 months in patients in whom such a resection was not necessary.
One case of invasion of the transverse colon from a tumor in segment VI was described by Hashimoto et al., who could find only 4 other cases in the literature. While hepatic invasion of the liver by a gallbladder cancer is common, invasion of the gallbladder from an HCC is rare. One case was reported by Tamura et al. in a M38. The tumor originated within segment IV-V. Wu reported another case.
A few cases of direct tumor invasion in the duodenum have been reported (review by Okusaka et al.).

Distant Metastases

Autopsy data are normally more accurate than clinical data, but they depend on the diligence of the pathologist, and reflect only the 'final' situation.
The rate of metastases is virtually unknown. At diagnosis it will amount up to 10-15%, but this will depend on the stage at diagnosis.
Of the 72 autopsied patients in the series of San José, 70% had extrahepatic metastases. Metastases were detected in 24/169 patients, or 14.2% in the series of Buscarini et al. It is not clear, however, if the figures relate to the number at diagnosis or at follow-up. Calvet and Bruix reported 14.2% at diagnosis.

Distant metastases from HCC are detected by the usual imaging methods. Specific molecules have, however, been developed for HCC. The use of Tc^{99m}-HIDA, an hepatobiliary tracer agent with specific uptake in the liver cell has been proposed for detecting (lung-) metastases of HCC. The results are disappointing, as only up to 30 % are visualized, providing late images are obtained (Wang et al.). The uptake depends finally on the functionality of the tumor cells and is usually lower when compared with the normal cells.
Another tracer, PMT or ^{99m}Tc-pyridoxyl-5-methyl-tryptophan, is taken up by hepatocytes and well-

differentiated HCC. Distant metastases have been demonstrated with this tracer (Fukui et al.). Mochizuki et al. have reported the detection of 21 of 26 metastases with SPECT, compared with 16 of 29 at planar imaging.

Metastases to the Spleen

Splenic metastases from HCC are very rare. According to Horie, they occur at autopsy in only 2%, in large series. They have reported on a patient presenting with an acute abdominal syndrome. The diagnosis of a metastatic HCC was made, but after 3 weeks, she suddenly died. At autopsy, a large splenic metastasis was found to have ruptured causing hemoperitoneum and death.
A similar case was reported by Al-Obaidi in a M65. In a case reported by Fujimoto et al., a control CT after a transcatether arterial embolization for an HCC showed an enlarged spleen, concomitant with uptake of Tc-tracer in spleen and bone metastases. The man died of a huge hemorrhagic spleen metastasis. They quote a Japanese autopsy study in which 3 of 439 patients or 0.7% had spleen metastases from HCC.

Metastases in the Gastro-Intestinal Tract

Metastases in sclerosed esophageal varices and within the tumor thrombi in the vessels have been described. They are considered as hematogenous but are probably reflux metastases along the portal vein (Hiraoka et al.). An autopsy study by Arakawa et al. disclosed tumor within varices in 23% of 55 cases.

Sohara et al. have apparently recently reported the first patients in whom esophageal metastases from an HCC have been observed at endoscopy and biopsy-proven. The most probable pathway is venous reflux from the portal system to the esophageal varices with resulting seeding in the submucosa.

The proximity of the liver to the stomach and duodenum, but also to segments of the colon allows direct invasion by the tumors. They are not true metastases and have been discussed above.
Metastases in the GI tract are infrequent, as peritoneal/serosal implants are not included.
Autopsy series reveal involvement of the stomach in 0.3 to 0.8% of HCC cases. Most were in the serosa; there were, however, some unusual cases involving the endolumen. DeNardi collected 4 cases from the literature, adding one. Recently, Lynch et al. claimed the first report of the endoscopic diagnosis of a submucosal metastasis. Green et al. have reported on one patient (M73) with two centrally umbilicated volcano-like masses in the stomach, one year after the diagnosis of HCC.
Upper GIT bleeding was the revealing sign of gastric metastases, confirmed at endoscopy, in two patients reported recently by Wang et al. Both patients had been diagnosed with HCC, one 6 years and the other seven months earlier.
Unlike those from contiguous invasion, true hematogenous metastases in the duodenum are rare. Arima et al. reported one case diagnosed by endoscopy and found three others in the literature. Upper gastrointestinal bleeding occurred in a prospective series of 55 patients with HCC. In three of them (6%) it was caused by duodenal infiltration by the tumor (Yeo et al.). A few other cases have been reported, all diagnosed after hemorrhage. Papillon et al. have recently reported on a M76 where hematemesis disclosed a duodenal tumor at biopsy, metastatic of an asymptomatic HCC.

Two cases of intestinal metastases have been reported (Narita et al.) They presented with multiple mucosal polypoid formations with hemorrhagic symptoms, typical for mucosal metastases. Another case was found at surgery necessary for intussusception of a nodular lesion in the proximal jejunum (Yang et al.). At autopsy of a woman dying at 73 of different pro-blems, 18 different intraluminal polypoid meta-static tumors were found in the ileum, some with long stalks. The histology was typical for HCC (Narita et al.).

Colonic metastases manifesting as GI bleeding are extremely rare. They can be the first sign of an HCC. According to Cosenza et al., reporting on one case, only two other should have been reported. They were all located in the ascending colon. The question to be asked is wether venous reflux along the portal system is responsible?

Metastases in the pancreas should occur in 3% of patients (Texler et al.). The incidence of spreading within the pancreas in patients coming to autopsy is 2.7 - 5.6% (Lowe et al.). They reported on a patient who presented with a localization in the pancreas head complicated by icterus, which led to the diagnosis.

Spread along Bile Duct System

Intrabile duct invasion is rare. Patients with a hidden or extended intrahepatic tumor present with progressive obstructive jaundice. A large part will involve a tumor thrombus within the bile duct. Kojiro et al. reported 24 observations in 1982. Wang mentions an incidence of 1.82% in 549 cases. In one autopsy series, 10% had growth in the bile duct system (Okuda). A number of case reports appeared later (Hamy et al.). One case should have been reported by Lau et al., with migrated tumor fragments within the bile ducts.
Another case was reported by Terasaki et al., where at autopsy of a F71, where tumor emboli in all branches distal from the portal vein up to the mesenteric vein were found associated with multiple tumor nodules within the bile duct up to the gallbladder, with a tumor mass filling the lumen of the gallbladder as well. As the gallbladder was not attached to the liver, it was not a contiguous growth.

Pleuro-Pulmonal Metastases

Lung metastases are quoted in all publications as being the most frequent after lymph node metastases. No report, however, has discussed the problem thoroughly, as far as size, site, number or other features of pathology are concerned.

Multiple tumor emboli in the pulmonary arterial tree, causing pulmonary hypertension has been reported in a few patients (see Chapter 1).This would appear a rare occurrence as up to 1984 only 5 cases were reported (Willett et al.).
Typical of HCC is that they can rupture, resulting in a hemothorax. Five pleural hemorrhagic cases resulting in catastrophic hemothorax have been reported up to 1996 (review by Akimaru et al. and by Takagi et al.).
Acute occlusion of several pulmonary arteries was seen at autopsy of a M52 who died suddenly after presentation in the emergency unit (Chan et al.).
One case of endobronchial metastases from HCC was mentioned in a series of 32 patients with these metastases by Salud et al., who gave no further details.

Pulmonary metastases occurred in 25% of the patients treated with transcatheter arterial embolization in the series reported by Liou et al. With other treatments, the incidence was only 8% (p=0.002). Lung metastases were usually found after a follow-up of about 14 months. The reason could be a modification of several hemodynamic, serological and biochemical factors modifying the metastatic proces. A number of clinical factors could be assessed as having a significant influence on the incidence of lung metastases (table 10.12). Several other factors such as age, gender, cirrhosis and type of agent were not found to be significant.
A recent clinical study by Katyal et al. (table 10.6) found the lungs to be the most frequent metastatic site (39%). They observed that in 83% of these patients, the size of the nodule was less or equal to 1 cm, while in the other patients, the size could attain 3cm only. The lower lobes were involved more often than the upper lobes (no data). Other extrapulmonary metastases were observed in 28% of patients with pulmonary metastases.

Table 10.12 - Hepatocellular Carcinoma
Factors influencing Lung metastases after TAE
Modified data of Liou et al. 1998

	Lung Meta	No Lung Meta
Tumor Type		
Solitary (>10 cm)	50.0%	17.2% (')
Multiple (main >5 cm)	17.5%	5.2%
Diffuse	20.0%	3.4%
Portal vein thrombosis	45.0%	13.7%
Arterioportal or arteriovenous shunt	42.5%	12.0%
Tumor Necrosis(>50%)	40.0%	7.7%

('): all significant p<0.001;
TAE: transarteric embolization

Bone Metastases

Skeletal metastases are relatively frequent. Depending on reports they will amount to between 2 and 16%. These metastases are more often accompanied by expanding soft tissue lesions than metastases from other primaries.
At autopsy, the incidence varies from 7.3% (Gattuso et al.) to 16.9% (Okazaki et al.).
They are aggressive lesions with a large propensity for cortical destruction and are nearly always osteolytic.
The aggressivity and the fast growth explains why only 60% are visualized at bone scintigraphy. Other 'hepatic' tracers (Tc-^{99m}-N-pyridoxyl-methyl-tryptophan) visualize more, up to 88%. IMP (N-isopropyl-iodo-amphetamine labeled with I-^{123}) was used by Suto et al. to detect pelvic bone metastases.

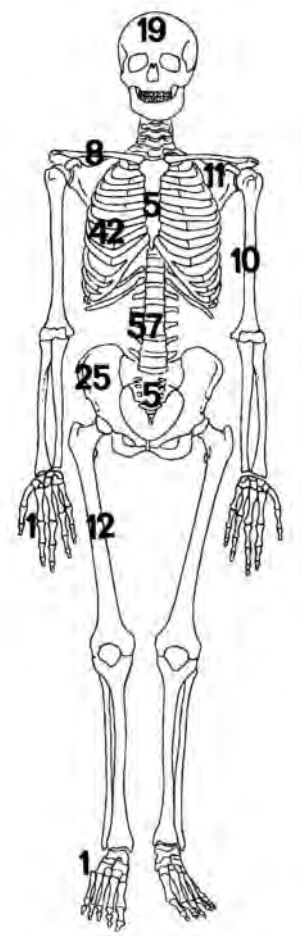

Fig.10.4 - Composite distribution of bone metastases in 107 patients.
Data from Okazaki et al.1985 (N=14); Kuhlman et al. (N22); Gattuso et al.1988 (N=10); Liaw et al.1989 (N=20)Nagata et al. 1989 (N=7); Taki et al.1992 (N=12); Maillefert et al; 1993 (N=22)

Striking is the relative frequently occurrence of bone metastases as first presentation. Maillefert even states that 50% of bone metastases are first clinical symptom of HCC. The reports are dispersed within the literature

Table 10.13 - Hepatocellular Carcinoma
Bone Metastases as First Presentation
Literature Review

Authors	Patient	Presentation
Skull		
Morvan 1976	M42	swelling parietal
Raghavaiah '77	M45	swelling parietal
Phadke 1981	M55	left frontoparietal
Tisdale 1985	M38	swelling frontal
Miura 1990	F37	swelling temporal > base
Shirashi 1992	M45	dysarthria : Condyle
Lee 1992	(6 cases)	(no details)
Sida 1993	M56	headache : parieto-occipital
Hirano 1995	M57	swelling fronto-parietal
Raoul 1995	F58	swelling parieto-occipital
Murokami 1995	M57	headache : Le.Petrous
Murokami 1995	M59	headache diplopia: petrous
Murokami 1995	M59	pain: sphenoid
Vertebral (+ Compression)		
Cayla 1971	M56	bilat.pyramidal: T7
Byrne 1972	M56	neck pain: C5-C6
Byrne 1972	M65	pain weakness C7-T1
Manigand 1974	M67	paraplegia T4
Yang1997	F47	limb weakness: T4-T5
Yang 1997	M37	low back pain: L1-L3
Cottin1981		7cases between T3 and S1
Vertebral		
Cayla 1971	M68	cervicobrach.pain : C5-C7
Cayla 1971	F54	sciatica : S1
Manigand 1974	M72	pain: L2
Shepherd 1984	F45	pain: lumbar and pelvis
Lee 1992		9 cases no further data
Kim 1998		5 cases between C5 and S1
Sternum		
Shepherd 1984	M61	swelling (many other meta)
Shiraishi 1992	M45	(second finding)
Jadaud 1997	M68	pain at cough
Rib		
Talerman 1973	M57	fracture rib 6
Manigand 1974	M51	incidental finding rib 6
Cottin 1975	???	#rib (1) and 3 osteolysis
Raghavaiah '77	M45	swelling chest wall
Chakravorty'77	M63	pain and swelling
Cottin 1981		no data
Nowak 1983	M61	pain+ mass rib 9
Soto 2000	M60	pain+ mass rib 7
Humerus		
Cayla 1971	M66	fracture
Cottin 1975	??	fracture
Robinson 1986	M56	pain left arm
Scapula		
Zeller 1986	M61	pain and mass
Golimbu 1985	M67	pain
Golumbo	M74	pain
Shiraishi1992	M45	(second finding)
Cottin 1975	??	---
Femur		
Cayla 1971	M49	pain
Talerman 1973	M17	fracture neck left femur
Shepherd 1984	M59	fracture
Raoul 1995	M69	fracture neck right femur
Iliac Bone		
Raoul 1995	M69	pelvic pain
Golimbu 1985	M73	pain ri.hip: ilium fracture

as the patients will present either to the neurologist (spinal or calvarian metastases), to the orthopedist as long bones or even to the stomatologist with oral metastases.

Of a consecutive series of 395 patients, 20 or 5% presented with bone metastases first (Liaw et al.). More than half were in the spine and the ribs. Spinal metastases can present with pain or even with syndromes of medullary compression. There is a slight predominance of lumbar vertebral localisations.
Metastases in the long bones such as the femur and humerus are not uncommon and more frequent than they are for other tumors (Kuhlman). Metastases in the cranial bones can be either in the skull, or in the cranial base. Peculiar is also that a number present with calvarian (skull) metastases first. Skull metastases have been reported to range from 0.5 to 1.6%, most cases occurring in men between 60 and 80 years old (Murakami et al.).

On the other hand, Taki et al. reported on 12 patients in whom bone metastases developed 1 to 36 months after hepatic resection. Here, the majority were also in the spine with 7 cases and 5 had pelvic metastases. There were also metastases in the rib, the sternum, the knee, the calvaria and the scapula.

Table 10.14 - Bone metastases in HCC
Compilation of 7 literature series
concerning 107 patients, with 199 sites

Skull	19	Spine (NOS)	57
Clavicle	8	Sacrum	5
Scapula	11	Pelvis	25
Sternum	5	Hand	1
Ribs	42	Foot	1
Humerus	10	(Long bones)	3

Skull	9.5%
Thracic skeleton	33.1%
Spine	28.6%
Pelvis-sacrum	15.0%
Limbs	13.5%

Table 10.13 shows the cases reported with revealing metastases. Table 10.14 (fig. 10.4) gives an overview of reported bone metastases in HCC from several series.The compilation of the data from several series allows a better insight into the distribution of bone metastases. It should be noticed that more than 60% of them are located above the diaphragm. There are indeed more metastases in the thoracic skeleton than in the spine.
A hemodynamic explanation is not directly obvious.
In several patients, the liver cancer was detected only weeks or months after the first metastasis.

Another interesting overview was published in 1971. Cayla et al. retrieved 48 reports on revealing metastases. They found half of the patients had spinal metastases. Almost half of the patients (49%) had at least

one metastatic site in the thoracic skeleton, while only 30% had a pelvic metastasis.

Metastases to the Head and Neck Region

This is a rare occurrence in HCC (table 10.15). Some cases have been included in series relating to bone involvement. Metastases in the skull base can be in the sphenoid sinus (Waxman et al.), in the orbit, or in the maxilla. Cranial nerve involvement might be the first symptom. Three cases presenting with sinusal (frontal, ethmoidal, sphenoidal) as first symptom of a HCC were reported by Mochimatsu et al.
A number of reports (nine) have appeared concerning gingival metastases. Half of them were type 1 metastases. Some reports do not distinguish between gingival and mandibular metastases. A review is not possible as most are in the Japanese literature.

Osteolytic metastases in the mandibula constitute a very particular clinical situation and location of bone metastases. In the 35 cases published up to 1997, 26 or 75% were the first sign of an unknown hepatocellular carcinoma. They occur most frequently in the sixth and seventh decade. It is striking that that there were only 3 female patients (Yoshimura et al.). In 40% of the cases, there were no pulmonary metastases, so that the so-called 'Batson's way' is the acceptable mode in its dissemination (Lalikos et al.).

Table 10.15 - Hepatocellular Carcinoma
Head and Neck Metastases Reported

Author	Patient	Site	Interval
Urvoy 1981	M59	Ethmoid	Revealing
Frigy 1984	M61	Le.Ethmoid	Revealing
Waxman 1985	M47	Sphenoid	Revealing
Knöbber 1991	M82	Ri.Nasal Cavity	Revealing
Mochimatsu '93	M67	Sphenoid	Revealing
	M40	Ethmoid	Revealing
	M67	Frontal sinus	Revealing
Sim 1994	M40	Sphenoid	Simultan.
Acenero 1995	M71	Tonsil	Revealing
Llanes 1996	M71	Ri. Tonsil	Revealing
Ciriza 1996	M71	Ri. Tonsil	3 years
Khayat 1997	M84	Maxill.Antrum	Revealing
Hayase 1999	M71	Hypopharynx	2 months
Izquierdo 2000	M59	Nasal Cavity	4 years

Gynecological Metastases

Up to 1992, five cases of ovarian metastases had been reported, of which three by Young et al. In these patients, diagnosis was made during follow-up and all had many other metastases. Differential diagnosis with so-called hepatoid carcinoma of the ovary and yolk-sac tumors is difficult. Another case was reported by Oortman et al.
Two years after hepatic resection and orthotopic resection, a woman aged 47 presented with a large pelvic mass. In spite of normal AFP, it turned out to be a large ovarian metastasis, without any other pathology in the abdomen (DeGroot et al.).

Silverman et al. mention one case of hepatoma metastatic to the breast in a F41.

Metastases to the Adrenal

At autopsy the incidence of adrenal metastases amount to 10/15% of all metastases (table10.4).

They are usually found at autopsy, but the more frequent use of CT and MR allows to find them more frequently in the living patient. Adrenal metastases indeed rarely evoke any symptom. Surgery can be considered in selected cases (Kitagawa et al.).
A review of the 35 reported cases of locally treated adrenal metastases from HCC has recently been reported (Taniai et al.). Half of them were solitary, 8 were found at presentation. No side preference has been noted. Only two were in female patients, which accords to the relatively low incidence of HCC in women. Size of up to 17 cm have been reported.

Another literature review disclosed 71 reported cases (Sakamoto et al.). Here the right to left ratio was 2:1. In 15, the diagnosis was concomitant and in 24 during follow-up. The 32 other were probably detected at autopsy, but this not stated in the review. Striking is the fact that the mean size of left sided adrenal tumors $(8.8cm \pm 4.37)$ was significantly larger than the right-sided $(6.1 \pm 2.8cm)$ at $p<0.05$. The authors relate this to the frequent overlooking of the left side during routine abdominal US-graphy.

A typical Addison presentation with brown hyperpigmentation in face, neck, elbows and palmar creases with typical endocrinological values suggesting an adrenal insufficiency was shown to originate from bilateral adrenal tumors concomitant with a large HCC. The final diagnosis was adrenal metastasis from the HCC (Takamura et al.).
One particular case resulting in a symptomatic hyperreninemic hypoaldosteronism has been reported (Otabe et al.). This was probably caused by unresponsiveness of the zona glomerulosa because it has been destroyed in both adrenals.

Scrutinizing the so-called pedunculated HCC or extrahepatic growth of HCC, a few authors have observed that the adrenal gland, with or without metastases where involved, will lead to a degree of hepato-adrenal fusion such as has been described in normal autopsies. These metastatic masses originate from an extra-hepatic hematogenous adrenal metastasis which becomes englobed in the enlarged liver. Reviewing the problem, Okuda et al. also noticed that of all adrenal metastases, two thirds were at the right. A particular difference in vascularisation could explain this. In a few patients, the preoperative diagnosis of an adrenal primary was even made (Ohwada et al.).

Cardiac Involvement

Cardiac metastases in HCC are found at autopsy in

about 2 to 5 % of the patients.
True myocardial metastases are rare. We are aware of one report involving the right ventricle wall, by Shyu et al. and one by Steffens et al. The latter patient presented with progressive dyspnea with signs of decompensation 5 years after surgery. An echocardiography showed a thickened ventricular septum with indication of a space-occupying mass in the right ventricle. At autopsy, a tumor in the wall of the right ventricle was found together with a large neoplastic embolus occluding a major branch of the pulmonary artery (fig. 10.5).

Table 10. 16 - Hepatocellular Carcinoma Vena Cava Tumor Thrombus Reported

Author	Patient	Symptom	Interval
Villet 1978	M59	Dyspnea	Simult.
Miller 1987	M30	Malaise	Revealing
Fujisaki 1991	F38	Dyspnea	Simult.
Kanematsu 1994	M55	Fatigue	Simult.
Ohwada 1994	F42	Malaise	6 months
Baba 1995	M81	Malaise	Simult
Yoshitomi 1998	M65	Hematemesis	Revealing
Yoshitomi 1998	M70	Abdom.pain	Revealing

Most tumorous cardiac problems encountered are intra-atrial or sometimes even an intra-ventricular exten-sion of a caval venous thrombus (table 10.16). In the case of Villet et al., the thrombus extended up to the arteria pulmonalis and histology of its branches also revealed an intravascular tumor.

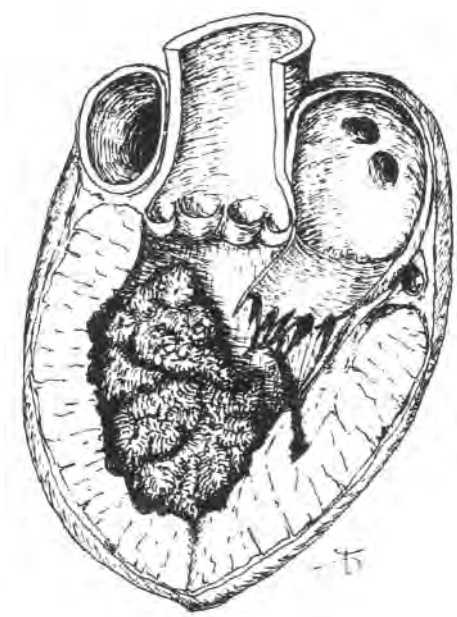

Fig.10.5 - Large metastases in the myocard of the right ventricle from a hepatocellular carcinoma.

Kojiro et al. reported on 18 cases verified at autopsy. A continuous tumor from the hepatic vein to the right atrium was seen in 15 cases. In the three other cases only the right atrium was involved. In 5 cases, the thrombus crossed the tricuspid valve.

Cutaneous Metastases

As is well known, skin metastases are frequently overlooked both clinically and at autopsy. Usually it is the patient who discovers the painful and/or hindering skin lesion. Skin metastases are frequently the top of the 'iceberg' of multiple other metastases. Only 48 cases should be known in the world literature up to 1995, but of these, only 31 were hepatocellular carcinoma, the others being a cholangiocarcinoma (Knight et al.).

The face and the scalp are the most commonly involved sites. Six cases are known of a solitary scalp metastases (Bakhomah). Some have been described at the puncture site of the hepatic biopsy (iatrogenic metastasis).
In the follow-up of a patient (M65), an umbilical metastases was detected (Raoul et al.).
The clinical presentations are papules, nodules, indurated plaques or inflammatory nodules. Some have an hemangiomatous or pyogenic aspect, bleeding heavily at incision. Two cases, one presenting as a pyogenic granuloma at the chin (Kubota et al.) and one at the nose were the revealing sign of a HCC (Berbis et al.). Another case (M62) reported by Yamanashi et al. presented at the cheek with a teleangiectatic granuloma two yearsafter the first diagnosis.

Metastases to the Central Nervous System

Brain metastases are rarely reported (Lee). One explanation could be the rapid fatal course of the HCC. They may also be overlooked in these patients where hepatic encephalopathy is diagnosed or supposed. Most should be found at autopsy, to the extent that the brain is examined.

Table 10.17 - Hepatocellular Carcinoma Cerebral Metastases reported

Author	Patient	Site of M	Interval
Chang 1979	M25	Ri.temporopariet.	Type1
Bitoh 1985	M52	Parasellar (first sign)	
Otsuka 1987	M71	Ri.frontopariet	
Uchino 1987	M45	Pons	
Lee 1988	F58	subdur.Le parasagittal	
	M59	Ri. parietal (hemat)	Type 1
Shuangshoti '89	M37	Ri. parietoOccip.	
	F56	Le.parietal	
	F25	Ri.temporopariet. subdur.	
Lee 1992	M59	Ri.fronto-parieta, hemorrh.	
Loo 1994	M13	Le.occipital hematoma	
	M38	Le.parietal hematoma	
Murakami 1996	16 cases	: 14 hemorrhagic site not given	
Kim 1998	7 cases	2 Type 1 4 stroke-like hemorrhage	

Note: some other cases have been reported in the Japanese literature, which is out of reach.

We were able to find about 40 cases in the literature of which one pontine and two meningeal (table 10.17). Almost all cases (80%) also had pulmonary metastases.
It is striking that brain metastases were the first presentation in 12 patients. More than 50% presented with apoplexy-like symptoms (Murakami et al). Many have been reported in the Japanese literature.
Of these 34 cases reported, 11/18 were at the parietal lobe or 60% of those with a known site. Two were at the cerebellum. The high number of cases where the symptomatology at CT was a hemorrhagic 'incident' (stroke-like) or hematoma presented as meningeal carcinomatosis.

Ophtalmic Metastases

The orbita as metastatic site is rare in hepatocellular carcinoma. Nevertheless a number of cases have been reported. Font et al. were able to collect 10 cases from the literature. In at least two patients, it was the presenting sign of an unknown HCC. The symptoms are mainly orbital pain with proptosis, but ophthalmoplegia and decrease of vision were also present. A case reported by Loo et al. as a metastasis in the orbit was probably a cerebral metastasis transgressing the frontal bone towards the orbit.
Most of the reported cases are type 1 presentations (table 10.18). There is probably a publication bias, because orbital metastases occurring in the follow-up are not so worthwhile reporting.

Table 10.18 - Hepatocellular Carcinoma
Ophthalmic (Orbit) Metastases reported

Author	Patient	Site of M	Interval
Lubin 1980	M69	Ri.orbit	Revealing
Zubler 1981	M64	Le.retroorb.	Revealing
Phadke 1981	M65	Ri.orbit	Revealing
Wakisaka 1990	M58	Le.orbit	Revealing
Schwab 1994	M19	Le.orbit	Revealing
Tranfa 1994	M85	Ri.orbit	Revealing
Font 1998	F79	Ri.orbit	Revealing
Scolyer 1999	M77	Ri.orbit	2 months
Barbat 2000	M57	Ri.orbit	Revealing

Metastases to the choroid in HCC are much rarer. Font et al. found only two reports in a literature. Yeatts et al. have reported on a M52 in whom HCC and choroid metastases were detected at autopsy.

Uro-Genital Metastases

Metastases from HCC within this system are very rare.
A cirrhotic man (M55) presented with gross hematuria. At CT, a large mass was found englobing kidney and adrenal, together with a prominent lobus caudatum and different lesions within the liver. It turned out to be an HCC with large metastases in the kidney invading the adrenal (Noble et al.).
A metastasis in the bladder dome was seen at cystoscopy after hematuria in a patient two years after liver transplantation (Franks et al.).
One patient presenting with testicular metastasis was reported by Young et al.
Very recently, Razi et al. reported on an apparently solitary metastasis to the glans penis in a man (M67), 10 months after partial hepatectomy.

Other Metastases

Boixeda et al. reported a case of HCC metastatic to a parathyroid adenoma. The patient presented with a HCC and hypercalcemia associated with a primary hyperparathyroidism. At autopsy, this was confirmed but he also had metastases in the adrenal, the lung and one in the adenoma of the parathyroid.

As fine-needle or trocard biopsy under imaging guidance is commonly used for the diagnosis, the risk of seeding is real. A number of cases have been reported. Reviewing the literature, Onodera et al. remarked an incidence of 0.005% in 63,000 cases. It seems that hepatic biopsy is much less prone to seeding than in malignancies such as pancreatic and gallbladder carcinoma. They recommend to include always normal liver parenchyma within the track in order to settle the neoplastic cells.

Causes of Death

About half of the patients will be found to have distant metastases at autopsy. This means that they die more frequently of complications due to liver failure and secondary troubles (table 10.19). Metabolic failure, cachexia due to under- or malnourishment, coagulation dysfunction are a large part of the causes. Bleeding from varices and rupturing tumors or metastases are not uncommon.

Table 10.19 - Hepatocellular Carcinoma
Cause of Death (N=1673)
Literature Compilation by Lee et al.

Liver Failure	34%
Hemorrhage (tumor, metastases, varices)	31%
Tumor death incl. cachexia	24%
Other causes (sepsis, respiratory,..)	11%

Overall Lesson

Although less frequent within the western world, the high frequency in the Far East and Southern Europe has yielded much information about this particular cancer. If hepatic self-destruction is the main problem, while distant metastases either as revealing or during follow-up have an uncommon pattern which may mislead the most attentive clinician.

METASTASES from CARCINOMA of the GALLBLADDER

Overall Pattern of Spread - Autopsy Study

Malignant tumors of the gallbladder evolve insidiously. Hidden virtually behind the liver, the gallbladder escapes clinical examination. Its anatomical position within peritoneal folds, its connection with the liver and the duodenum through the bile ducts and tits proximity to several important organs will lead to the possibility of various types of spread.
Imaging methods, surgical exploration and autopsy studies show that the organ that has the greatest overall frequency of involvement is the liver. Gallbladder cancer is indeed primarily a local and regional 'problem', while distant metastases are more the exception than the rule. The autopsy study reported by Sons et al. clearly shows the importance of local and lymphatic spread (table 10.20).

Local Evolution

Gallbladder cancer spreads along 6 ways:
- the lymphatic vessels,
- the various other vessels,
- intraperitoneal,
- along the nerves,
- intraductally and
- by direct invasion of the liver and of the intestine

Early spread is a consequence of the microscopic structure of the gallbladder wall. It lacks a submucosa and has only a thin mucosa and single layer of smooth muscle. This results in a weak barrier against tumor infiltration. Further invasion of the muscularis brings the cells in direct contact with subserosal tissue, from where they gain access to blood and lymph vessels irrigating neighbouring structures.

As such symptoms may be present which could be at first sight be due to a cancer of organs such as pancreas, duodenum or stomach. Moreover, perforation occurs in a small number. This can also lead to peritoneal, mesenterial or omental seeding and metastases up to the abdominal wall (umbilicus).
One particular threat is the direct invasion of the tumor in the liver from the gallbladder bed, as the gallbladder lies in the fossa felea. At autopsy, 60% of the cases showed liver invasion (fig. 10.6).

Fig.10.6 - Extension of gallbladder cancer to the liver A. through the hepato-duodenal ligament; B. through regional lymphatics or cystic veins; C. through direct hepatic involvement. (Ohtsuka et al., with permission)

Intraductal spread has been described in about 20% of papillary tumors (Fahim).
Contiguous spread will be very likely due to the close contact the gallbladder has with surrounding structures. Invasion of the colon and/or the duodenum occurs each in about 15% of cases each.

Lymphatic Spread

As for the other upper gastrointestinal cancers, the lymph node stations have been extensively studied by Japanese surgeons and anatomists. They are all codified as follows (fig. 10.7):
Along the right side of the hepatoduodenal ligament: 12b -13 - 12p -16; Along the left side : 12a - 8 - 12p - 9 - 16. The code-number of the LyNo is according to the Jap.Bil.Soc. A thicker line illustrates the most frequently followed route, as plotted from a series of patients.

Table 10.20 - Carcinoma of the Gallbladder
Metastases found at Autopsy in 287 patients 1950-1982
Study of Sons et al. 1985

Distant		Infiltration per continuitatem		Lymph nodes	
Liver	66.2%	Liver	64.8%	l.n.cervicales	1.4%
Lungs	15.3	Colon	15.3	l.n.supraclaviculares	2.4
Bone	9.4	Duodenum	14.6	l.n.axillares	0.7
Heart	6.3	Pancreas	6.3	l.n.paratracheales	4.2
Pancreas	5.2	Bile ducts	3.5	l.n.peribronchiales	4.5
Kidney	4.9	Omentum minus	3.1	l.n.para-oesophagales	2.4
Adrenal	4.9	Vena portae	3.1	l.n.portales	57.1
Colon	2.8	Stomach	2.8	l.n.hepatici	28.0
Brain	2.4	Omentum Maj	2.1	l.n.paragastrici	7.7
		Vena lienalis	1.4	l.n.parapancreatici	19.5
		Mesenterium	1.0	l.n.pancreaticoduodenales	4.9
				l.n.mesenteriales	11.1
				l.n.paraaortales abd.	28.2
				l.n.para-iliacales	1.0
				l.n.para-ovariales	0.3

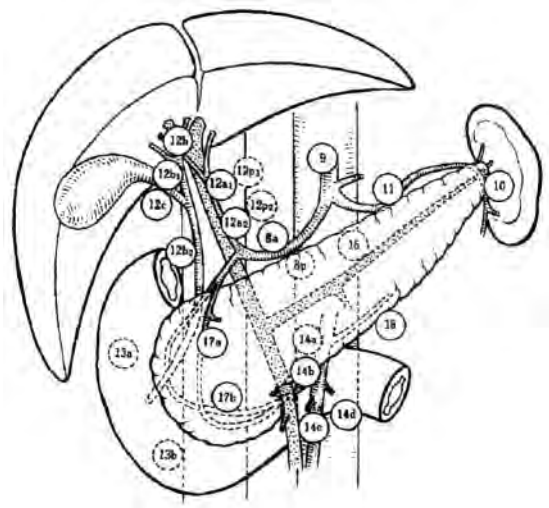

Fig. 10.7- Lymph node classification and Code according to the Japanese Society for Biliary Surgery (1986)

Table 10.21 - N-classification by UICC-TNM
Regional lymph nodes (N)

Nx regional lymph nodes cannot be assessed
N0 no regional node metastasis
N1 Regional lymph node metastases
N1a metastasis in cystic duct, pericholedocal, and/or hilar lymph nodes (i.e. in the hepatoduodenal ligament)
N1b metastasis in peripancreatic (head only), periduodenal, periportal, celiac, and/or superior mesenteric lymph nodes.
At least 3 nodes have to be examined.
(N2 is not attributed in the TNM-system)

Lymph node metastases are first regional, then up to the hepatoduodenal ligament and even further either abdominally or intrathoracic, up to the supraclavicular region.
The UICC-TNM classification is shown in table 10.21.

Collecting trunks present on both the left and right borders and diagonally to the left side of the neck. Most of the collecting trunks on the left side terminate in the cystic node, which lies along the left side of the cystic duct in the acute angle formed by the junction of the cystic duct and the common hepatic duct. The collecting trunks at the right side of the gallbladder pass along the right border of the neck of the organ and extend without interruption to end in the pericholedochal nodes. The efferent vessels of the cystic node and of the uninterrupted lymph vessels of the gallbladder drain to two principal nodes along the common bile duct (Fahim). These two pericholedocal nodes are the node of the hiatus and the superior pancreaticoduodenal node.

The hiatus node is usually to the right of the common duct in the lesser omentum, with its upper end a few millimeters below the origin of the common duct and its lower pole lying in the attachment of the lesser omentum behind the superior portion of the duodenum.
The superior pancreaticoduodenal node is relatively large and is situated in the angle between the first and second portions of the duodenum, along the superior surface of the pancreas to the right of the common duct. From this node, the routes are either towards the origin of the celiac artery, or via the posterior pancreatoduodenal nodes around the vascular arcade in the posterior pancreatoduodenal groove.
From here they drain to the chain of nodes around the origin of the superior mesenteric artery. Some authors dreject the possibility of a drain to the hilus of the liver.

Other authors identify three pathways:

-Cholecysto-retropancreatic pathway, with vessels on the anterior and posterior surface of the gallbladder, converging to a large retroportal lymph node. This node communicates with the choledochal and pancreaticoduodenal lymph nodes.

-The cholecystoceliac pathway runs from the gallbladder to the left through the hepatoduodenal ligament to the celiac nodes.

-The cholecysto-mesenteric pathway runs to the left in front of the portal vein and then to the pancreaticoduodenal and aorticocaval nodes.

Shirai et al. simplified this as follows: the regional lymph nodes include those along the bile duct, the second station is at the nodes posterior to the pancreas and finally, the interaortocaval nodes adjacent to the left renal vein (fig. 10.8).

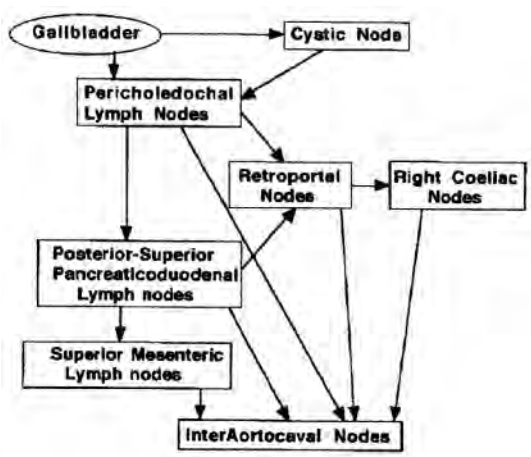

Fig.10.8 - Diagrammatic representation of the regional lymph nodes of the gallbladder. The arrows indicate the principal routes and the direction of flow. The arrows indicate probable routes. (Shirai et al.)

Table 10.22 - Carcinoma of the Gallbladder
Depth of Invasion and Lymph node Metastases
Data of Tsukada et al.

	N	N1	N2	P.A.	Total
T1	15	0	0	0/4	0
T2	46	14	8	3/23	22 (48%)
T3	25	6	12	5/16	18 (72%)
T4	20	4	12	4/18	16 (80%)
All	106	24	32	12/61	26 (53%)

(P.A.: Para-aortic nodes)

Tsukuda et al. stressed the correlation of nodal metastases with the local extent of the tumor (table 10.22). More recent details on their patients were published recently and are summarized on table 10.23. The number of invaded nodes clearly parallels the tumor extension. The cystic and pericholedocal lymph nodes have the highest rates of invasion, more than 25%.

More data have been provided by Shimada et al. according to the LyNo Nr of the Jap.Soc.Bil.Surg. (table 10.24).

Based on a meticulous dissection and study on 41 patients, Shimada et al. traced the lymph flow between the involved nodes and also concluded that there were both right and left routes (fig. 10.9).

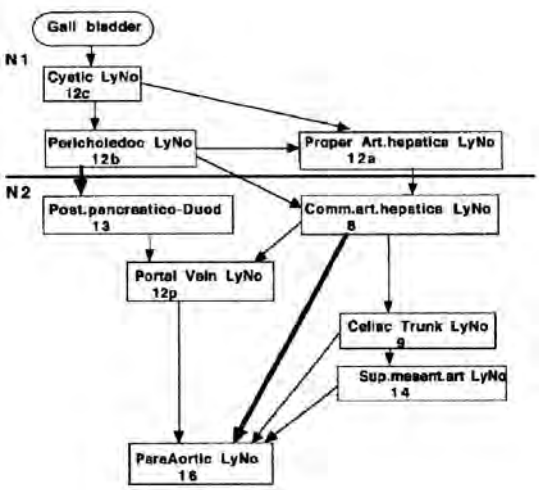

Fig.10.9 - The close relationship between the metastatically involved lymph node stations (redrawn from Shimada).

Table 10. 23 - Carcinoma of the Gallbladder
Prevalence of Lymph Node Metastases
according to T-grade (Tsukada 1997)

Lymph Node	T2 tumors	T3-4 tumors
N1		
Cystic Ly No (12c)	33%	17%
Pericholedocal (12b)	15%	50%
Hepatic hilar	--	--
Periproperhepatic	4%	15%
Retroportal (ceph.)	2%	6%
N2		
Retroportal (caud.)	8%	27%
Post.sup.pancr.duod.(13)	6%	23%
Ant.comm.hepatic	2%	17%
Post.comm.hepat.	5%	19%
Celiac node (9)	0	25%
Post.inf.pancr.duod.	0	4%
Sup.mesenteric (14)	0	13%

Hepatic Metastases

The liver is involved in gallbladder cancer in two ways: firstly and most commonly by contiguous invasion from the fossa vesicae felleae and secondly through hematogenous seeding via vena portae.

At the microscopic level, Ohtsuka et al. could distinguish three patterns:

1. tumor cell nests confined to the portal tract;
2. nodular type, well defined without obvious invasion of the portal tract;
3. a combined pattern.

This must be distinguished from contiguous hepatic invasion.

Table 10. 24 - Carcinoma of the Gallbladder
Frequency of lymph nodes (Shimada)

Site (Nr)	Group	Frequency
Cystic (12c)	N1	19.5%
Pericholedocal (12b)	N1	41.5
Around proper hepatic duct	N1	9.8
Around portal vein	N2	22.8%
Post.pancreat.duodenal	N2	36.6
Around comm.hepatic artery	N2	22.0
Around celiac trunk	N2	(5/18)
Around super.mesent.artery	N2	(3/16)
Paraaortic	(N3)	(7/27)
(There were 4 pT1, 21 pT2 and 16 pT3/T4)		

Invasion of the portal tract occurs in several ways (fig. 10.10) (Ohtsuka et al.):

1. directly through the hepatoduodenal ligament, by stepwise invasion of the lymph nodes to the portal tract;
2. through the regional lymphatics and/or cystic veins in the liver;
3. direct hepatic involvement.

The most important route of early hepatic metastases is probably portal tract spread through peripheral liver invasion. Ogura et al. have identified three specific patterns of invasion (fig. 10.10). It would seem that type A is very rare.

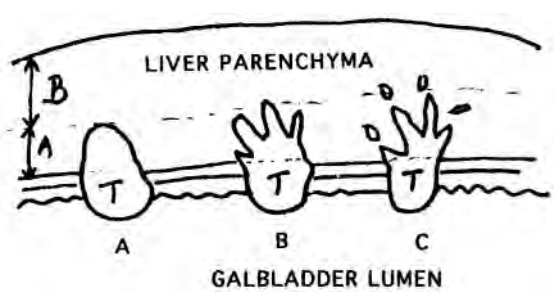

Fig.10.10. - Gallbladder Cancer: Patterns of liver invasion a. expansive pattern; b.infiltrating and continuous pattern and c. infiltrating discontinuous. A is the distance between liver bed and cancer front and B is the distance between cancer front and resection margin (Redrawn from Ogura et al.).

Type B (expansive) is encountered only in the liver-bed type cancer, whereas the C or the infiltrative type is found in both liver bed and hepatic hilar types.

Distant Metastases

Distant metastases probably originate from the invasion of the retroperitoneal veins and are usually rare. They may occur anywhere in the abdomen and elsewhere in the body, though have a preference for the liver (table 10.25).

Table 10.25 - Carcinoma of the Gallbladder
Sites of metastases(N=43)
Series of Brandt-Rauf 1982

Lymph Nodes	65.1%	Uterus(')	(2 cases)
Liver	81.3	Bladder	2.3%
Peritoneum	34.8		
Intestine	32.5	Diaphragm	18.6
Omentum	18.6	Lung	27.9
Pancreas	16.2	Heart	6.9
Adrenals	13.9	Bone	11.6
Kidneys	9.3	Skin	4.6
Ovaries(')	(4 cases)	Pleura	4.6
Retroperitoneal	6.9	Thyroid	2.3
Ureter	4.6	Meninges	2.3
Spleen	4.6	Muscle	6.9

(') the number of female patients is not stated

A few literature series have reported the incidence of distant metastases. The data are shown in table 10.26. There is a certain consistency, but it depends on the registration method and the diligence of the clinician and pathologist. Overall, metastases beyond the liver are not so frequent, as only the lungs are frequently enough involved to be listed.

Table 10.26 - Carcinoma of the Gallbladder
Sites of metastases in recent series

	Shukla 1985	Chao(') 1991	Ruckert 1996	Chao(') 1996
Location	N=150	N=51	N=81	N=52
LyNo at porta	52%	53	--	38
Distant LyNo	--	30	--	10
Hepat.duod.ligam.	--	8	47	15
Liver	85	76	56	51
Lungs	--	26	--	--
Oment-Perit	22	12	31	15
Mesentery	8	--	--	--
Omentum	--	12	31	15
Stomach-Duoden	6	--	--	--
Stomach	--	--	6	2
Duodenum-colon	--	8	17	12
Colon	--	6	--	12
with ascites	10	6	--	8
Pancreas	--	14	5	2
Kidney/adrenal	--	6	3	--
Ovary	--	--	--	4
Uterus	--	--	--	2
Spleen	--	6	--	--
Small intestine	--	6	--	--
Others	--	25(*)	--	--

(*) adrenal, thyroid, brain etc.
(') The 1991 series of Chao concerns patients in Chicago and that of 1996 patients in Taiwan.

Several unusual presentations have been reported:

A patient presenting with hemobilia because of erosion by the gallbladder tumor of the hepatic artery and forming a fistulous communication was reported recently by Jones et al.

Intraperitoneal seeding is quite rare except where it involves late and direct invasion of adjacent structures such as the colon, the duodenum and the stomach (10-20%). However, this form of spread has recently increased, following laparoscopic cholecystectomy.

Metastases to the Central Nervous System

A man of 59, presenting with hemiballismus, was found at autopsy to have a gallbladder cancer with thalamic metastases (Lemmen et al.).
A case with metastases in the dural and epidural space, a few months after the diagnosis of a small gallbladder carcinoma was reported by Newman et al. in 1977.
Burgess et al. reported one case presenting with acute spinal cord compression due to metastatic deposits, in the the dorsal spine. They had also two patients presenting with skin metastases.
A man presenting with a brain tumor simulating a meningioma was found to have a metastatic gallbladder cancer (Kawamata et al.). The rare sagittal sinus thrombosis was the first sign of cancer of the gallbladder in a woman of 58 (Smith et al.).

Tans et al. reported a patient presenting with meningeal carcinomatosis. They found 4 other cases in the literature, but more have been reported. The particularity is that almost all were type 1 presentations (table 10.27), in whom the diagnosis was made only at autopsy.

Table 10.27 - Carcinoma of the Gallbladder
Leptomeningeal Carcinomatosis
Cases reported in the literature

Author	Patient	Presentation
Brucher 1960	M64	Autopsy Revealing
Stark 1986	M45	Postoperative evolution
Naylor 1988	M71	Autopsy-Revealing
Honma1990	F57	Autopsy-Revealing
Birouk 1992	F56	Surgery Revealing
Pedrazolli 1992	F61	CSF-CT-Revealing
Tans1993	F60	Autopsy-Revealing
Gaumann 1999	F78	Autopsy-Revealing

The pathway could be a matter of debate. Dissemination along perivertebral plexus (Batson) must be considered, as in many cases, peritoneal spread was also found.

Gynecological Metastases

Up to 1992, there were 57 cases of gallbladder cancer reported with metastasis in the ovary, of which 10 from the relatively infrequent cystic duct primary (Lashgari et al.).

The histology type of signet-ring cell adenocarcinoma has apparently the highest propensity to metastasize at that site (Lashgari et al., Young et al.). Schust et al. reported 2 cases presenting with metastases in the uterus as first sign. They found four other cases in the literature.

Other Metastases

Cutaneous metastatic adenocarcinoma at the forehead and neck, upper arms and back, together with axillary and submandibular region and lung metastases were the first sign of a gallbladder carcinoma in the patient reported by Krunic et al. A few cases of solitary skin metastases in the follow-up have been reported (Bardaji et al.). A large scalp tumor was the first sign in a 46 year old women (Pandey et al.).
Padilla et al. reported a women presenting with multiple skin metastases over the head and neck, where clinical examination also disclosed an obstructive icterus. A few cases with umbilical metastases unre-lated to laparoscopic procedures have been reported (Figer et al.).

Two cases have been reported where the gallbladder tumor was found after resection of a metastatic tumor in the ureter (Sarma et al.). This was most probably a case with a downward retroperitoneal spread. An earlier case reported involved an obstruction caused by retroperitoneal nodes. The gallbladder cancer was found at laparotomy (Claire et al.).
From table 10.25 one can remark that bone metastases are not mentioned. At autopsy, however, (table 10.19), Sons found that 10% of the patients had bone metastases.

We are aware of only one case with H&N metastases, a 67 year old female with palatine tonsil metastases three years after surgery for an advanced cancer (Asami et al.).

We found references to metastases to the orbit (Saxena et al.), the left supraclavicular node (MacCusick, 3 cases as first presentation) and in the umbilicus. In a series of 327 patients, Harinhakti et al. found 11 patients with left supraclavicular node metastases, 1 with an inguinal node and one with umbilical metastases. An orbital metastasis was reported by Bulloch et al.

Up to recently, only 4 cases have been reported with cardiac metastases, of whom two patients with a squamous carcinoma of the gallbladder (Suganuma et al.); a peculiar histology indeed.

Mucin-thrombotic endocarditis with embols to the lung and within the inferior vena cava with tricuspid vegetations from a gallbladder carcinoma has been reported in a M57 by Min et al.
Pulmonary metastases of the rare cavitary type were the first sign and unique metastases of a gallbladder adenocarcinoma in a 63 year-old man (Baba et al.).
A number of cases have been described where the tumor protuded from the gallbladder through the cystic duct into the common duct as a mucinous tumor thrombus. This is a very rare cause of ob-structive jaundice (Midorikawa et al.).
Finally, the cutaneous recurrences at the umbilicus or at the port-sites after laparoscopic resection of an incidental galbladder cancer must be mentioned.

Overall Lesson

Cancer of the galbladder is a local growing and invading process with involvement of liver and the upper gastrointestinal tract and colon transversum.
Distant metastases are rare, but the number reported of presentation with metastases first is disturbing, especially in the life-treatening presentation of leptomeningeal carcinomatosis.

METASTASES of CANCER of the BILE DUCT

Spread

Bile duct cancer spread frequently spread along the wall of the duct and will invade the duct system distally but also proximally to within the liver, mainly in the lobus caudatus. This is due to the fact that the bile ducts enter the main left or right hepatic duct within one cm. of the hepatic duct. Even a small tumor arising at the hilus of the liver (Klatskin's tumor) can extend into the bile ducts draining the caudate lobe (fig. 10.11).

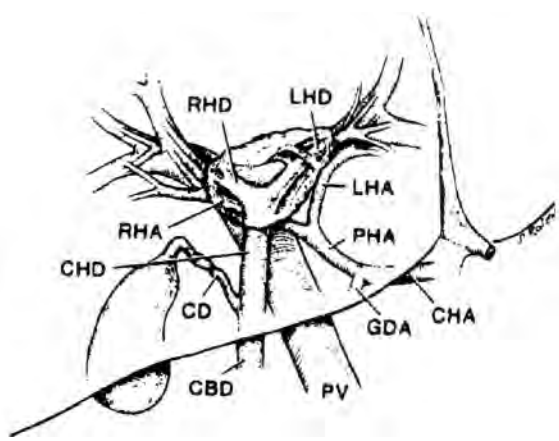

Fig.10.11 - Anatomy of the hilus region demonstrating the intricacy of the structures and the high likelihood of invasion of a hilar tumor (from Lee et al., with permission).
RHD and LHD: right and left hepatic duct; *RHA and LHA*: right and left hepatic artery; CHD: common hepatic duct; CD: cystic duct; CBD: ductus choledocus; PV: vena portae; PHA art. hepatica; GDA: art. gastroduodenalis; CHA art.hepatica communis

Pathology studies can detect the following :
- spread along duct walls and periductal tissue
- vascular invasion, mainly veins
- lymphatic involvement
- neural and perineural invasion
- direct intra-sinusoidal invasion of tumor cells between plates of hepatocytes (Weintreib).

The mode of spread is definitely related to the gross aspect and histology, but also to the original site of the tumor. This has been extensively studied by Yamaguchi et al. Although the number examined was rather small (N=46), certain features could be observed and are summarized below. Additional data have been provided by Sakamoto et al. More distally located tumors will invade the pancreas.

Histology (Yamaguchi): 67% of upper tract duct are papillary or well-differentiated tubular adenocarcinoma of the polypoid or nodular gross type.
64% of lower bile duct are moderate or poorly differentiated tubular adenocarcinoma
Invasion (Yamaguchi): Perineural spread occurs in 75% of upper bile duct, lymphatic permeation and venous invasion in 50% op upper, but 73% of lower tract cancer. Lymphatic metastases are more frequent in lower tract tumors.
Periductal spread towards the liver is more frequent in the infiltrative type than the polypoid or nodular type.
Submucosal spread has not beenobserved in the polypoidtype.
Involved layer (Sokamoto):
Mucosa: The leading edge of the infiltration is mucosal in 27% and in 73% submucosal.
Significant mucosal spread was most frequent in papillary cancers. The longest extension was 31 mm.
Submucosa: is the most common (60%) and is characteristic of the infiltrative or nodular-infiltrative tumor, along with lymphatic invasion.
Perineural invasion extends, primarily in hilar cancers, distally and perpendicularly through the peri-neural space and often involves the autonomic nerve plexus around the hepatic artery (Sakamoto).

Node Metastases

The regional lymph nodes are the same as those listed for the gallbladder, but include those located near the duodenum and head of the pancreas. They include the following (fig. 10.12):
cystic, hilar, superior mesenteric, periduodenal, node of the anterior border of the foramen of Winslow, superior retropancreaticoduodenal, posterior pancreaticoduodenal, peripancreatic, periportal, pericholedochal, celiac.

As well as some differences in lymphatic spread according to the location of the primary tumor, the lymphatic spread is not always limited to the area around the primary tumor and within the region excised. The literature states that at least 30% of the patients will have nodal metastases at diagnosis, but many series report a higher percentage.

The proximal and middle bile duct carcinomas display basically similar patterns of nodal involvement above the suprapancreatic border.
The frequency of involved nodes along the proper and common hepatic artery increases in proximal tumors compared with middle carcinomas. The lymphatic pathway along the common hepatic artery will predominate over that to the superior retropancreaticoduodenal glands when there is involvement of the hepatoduodenal ligament (N2).

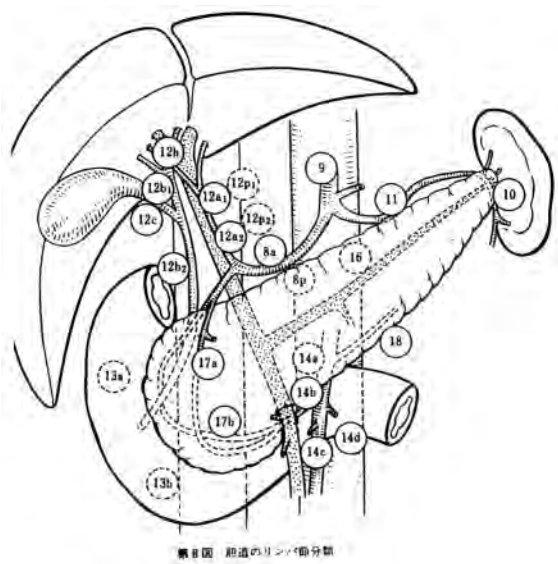

Fig.10.12 - The lymphatic drainage of the biliary tract, as coded by the Japanese Society for Hepatobiliary Surgery. (See fig.10.15 for further details)

In middle duct carcinomas, the nodes are distributed in the most widespread pattern in the three groups and include nodes around the superior mesenteric artery and para-aortic node. It is thought that the para-aortic nodes receive metastases via the right lymphatic route of the hepatoduodenal ligament (fig. 10.13).

Table 10.28 - Cancer of Extrahepatic Bile Duct Frequency of node involved according to local extent of tumor (TNM) (Kurosaki et al.) (N=80)

	T1	T2	T3	T2&3
Proximal	0/1	3/7(43%)	7/14(50%)	10/21(48%)
Middle	0/2	8/16(50)	16/20(80)	24/36(67)
Distal	0/4	2/5 (40)	7/11(64)	9/16 (56)

The frequency of node metastases according to the local extent of the tumor is shown in table 10.28.
In distal carcinomas, the lymph node involvement is strongly influenced by the pancreatic invasion, with a high frequency of metastases to the superior mesenteric node, though usually restricted to around the head of the pancreas.
The nodes occurring with tumors of the distal bile duct have been studied extensively by Yoshida et al.

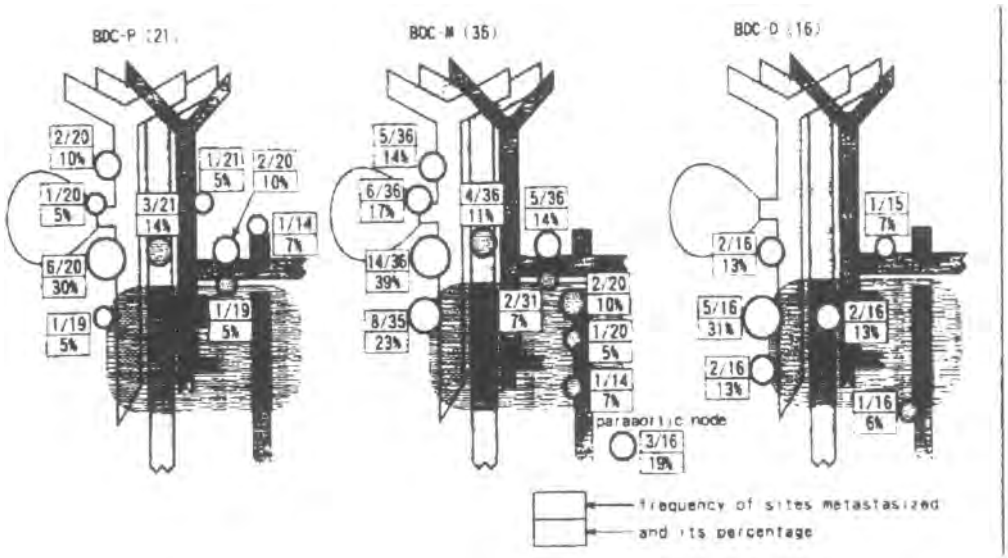

Fig.10.13 - Comparison of the lymph nodes involved and spread according to the location of the primary tumor. (BDC-P : proximal; BDC-M: middle; BDC-D:distal) (Kurosaki et al. 1996, N= 80,with permission)

Table 10.29 - Cancer of the Distal Bile Duct
Lymph node metastases
Data of Yoshida et al.

Overall : 25/42 (60%)
pT2: 5/12 (42%)
pT3: 20/26 (77%)

Group(')	pT2	pT3
6	0	1 (4%)
8	1 (8%)	5 (19%)
12	3 (25%)	14 (54%)
13	4 (33%)	13 (50%)
14	0	6 (23%)
16	0	6 (23%)
17	0	3 (12%)

(') in the other groups no metastases found.

Their latest report stress the invasion of the pancreas with lymphatic spread from the hepatoduodenal ligament or into the posterior pancreaticoduodenal region up to the superior mesenteric and the para-aortic nodes (table 10.29).
Groups 8 (around hepatic artery), 12 (hepatoduodenal ligament) and 13 (posterior pancreaticoduodenal) are the first involved nodes, for tumors of the lower bile tract. This is almost never addressed in the reports on biliary duct cancer, exceptin relation to liver metastases (with very few data).

Recently, interesting data were published by Kitagawa et al. Of 110 patients with hilar cholangiocarcinoma enrolled in a study to examine the nodal incidence, 52 or 47% had negative node dissection. The data obtained in the 58 other aptients are shown in table 10.30. The authors stress that in 17.3% paraaortic nodes were involved, more than in the posterior pancreaticoduodenal nodes. The progression from T2 to T3 results in a higher number and more non-distal involvement.

Table 10.30 -Hilar Cholangiocarcinoma
Incidence and Site of Lymph Node metastases (N=52)
Resection Data of Kitagawa et al.

	pN1-N2 N=39	pM1 N=19
N1		
Pericholedocal (12h, 12c,12b)	79.5%	84.2%
N2		
Periportal (12p,12a)	46.2	84.2
Common hepatic (8a,8p)	46.2	63.2
Poster.pancreaticoduod. (13a)	20.5	42.1
Celia (9)	2.6	31.6
Super.Mesenteric (14)	--	(57.1)(')
M1 (N3)		
Para-aortic	--	(100%)
Paragastric- paracolic	--	(60%)

(') too low for significance

pT2 (N=42)	11(26.2%)	3 (7.1%)
pT3 (N=68)	28 (41.2%)	16 (23.5%)

Distant Metastases

Bile duct cancer kills more by locoregional invasion in the neighboorhood than through distant metastases. According to Marcos-Alvarez et al., spread to extra-abdominal sites is uncommon. Okuda et al. in an autopsy study of 57 cases of intrahepatic bile duct carcinoma found metastases in the pancreas (10%), adrenal gland, spleen, stomach, but in more than 22% in the lungs.
Peritoneal spread is, in fact, unusual, except in some situations as described by Tanaka et al. They observed that when bile duct cytology was positive, the risk of subsequent peritoneal implants was very high. The bile duct should, particularly if bile cytology is positive, be clamped before section.

Bedikian et al. report 7 cases with distant metastases

of which 3 in the colon, 1 in the duodenum, 1 in the stomach and 1 in the bone marrow, the last case being the only one with extra-abdominal metastases.

Recently, a patient (M68) was reported presenting with ataxia and hemianopsia 6 years after surgery to have a solitary cerebellar metastasis removed(Tanaka et al.).
A metastatic cholangiocarcinoma masquerading as a primary ovarian carcinoma was reported by Sharma et al.
A case was reported by Mann et al. of an acute appendicitis in a patient 14 months after the diagnosis of a cholangiocarcinoma in the distal part. It was treated only by insertion of a metallic stent into the left hepatic duct. The appendicitis was caused by a metastatic tumor of the same histology. Patients with a recurence within the abdominal scar have also been reported (see Mittal et al.).
Marcos-Alvarez et al. state that at least 50% of patients harbor aggressive tumors with early death from diffuse peritoneal metastases being likely.
In his series of patients presenting with leptomeningeal carcinomatosis, Brucher (1960) mentions one case (M54) of choledochal carcinoma revealed at autopsy. A recent case, involving leptomeningeal metastases whose course was fulminant has been reported (Huffman).

In another case, an enlarged painful testicle was found to contain an adenocarcinoma. At autopsy following sudden death after surgery, the testicle was found to be one of several metastases of a cancer of the common duct (Grignon et al.).

Eighteen months after surgery for a common bile duct cancer, a M69 presented with right eye swelling, with ptosis of the upper eyelid and a tender hard metastatic mass superolaterally in the right orbit (Bullock et al.).

In a patient (M73), Ueda et al. described multiple skin nodules over the left abdomen, occurring five months after surgery for a tumor at the bifurcation of the common duct. They were probably cutaneous seeding favored by long-standing placement of percutaneous drainage tubes.

METASTASES from CARCINOMA of the PANCREAS

Hidden behind the posterior peritoneal wall and within the retroperitoneal space, carcinoma of the pancreas will develop unnoticed and tend to invade the neighbouring organs lying within the same space (table 10.31).
True distant metastases are not frequent or are poorly documented except a few autopsy reports. This probably correlates with the low metastastic intensity of pancreas cancer.

The discussion has been limited to the adenocarcinoma, the histological type most frequently encountered, occurring in more than 95% of the cases.

Table 10. 31 - Cancer of the Pancreas
Pathways of Spread

1. Contiguous invasion of neighbouring organs
2. Transperitoneal invasion
3. Spread into the retroperitoneal lymph nodes
4. Hematogenous spread after venous embolization.

The retroperitoneal neighbouring organs are the duodenum, the stomach, the transverse colon, the diaphragm and the spleen. After transperitoneal invasion, the ovaries, the peritoneum itself, the omentum, and the mesenterial surface of small bowel can also be involved.

Autopsy Data

The relative proportion of the different pathways of spread can be evaluated from autopsy data (table 10.32). However, the autopsy series however consist of different kinds of patients, some not operated because of advanced disease and other surgically treated, having opened the peritoneum and allowing further spread.

Table 10. 32 - Cancer of the Pancreas
Metastatic Spread - Autopsy Data (N= 94)
Modified from data of Kishi et al.

Retroperitoneal		Distant metastases	
Lymph nodes	80.9%	Lungs	52.1%
Retroperit.spac	24.5	Vertebrae	12.8
Diaphragm	31.9	Pleurae	7.4
Duodenum	33.0	Gallbladder	7.4
Stomach	31.9	Ovaries	5.3
Peritoneum	38.3	Heart	4.3
Kidneys	9.6	Uterus	3.2
Ureters	4.3	Urin.Bladder	2.1
Adrenals	24.5	Skin	2.1
		Spermatic Cord	1.1
Intra-Abdominal		Thyroid	1.1
Liver	72.3		
Bile Ducts	29.8		
Great Omentum	13.8		
Mesenterium	9.6		
Spleen	11.7		

When the incidence of metastases is correlated with the site within the pancreas, one can remark that metastases are somewhat more frequent for cancers of the body and tail than for tumors at the head. This is generally the case for all the retroperitoneal organs except the duodenum and can be explained by the anatomical situation.

In another study, Douglass et al. pointed to the fact that in 47% of 108 patients, three types of metastatic spread within lymph nodes, transperitoneally and hematogenous was found, while only one kind was

found in 12%. They also observed that metastases to the bone marrow were frequently a prelude to bone metastases in more than two-thirds. Wide abdominal spread was noted in 80%.
The conclusion that can be drawn from this is that in an overwelming majority of cases, cancer of the pancreas spreads mainly within the abdomen, and has a proportionally low rate of hematogenous metastases.

Contiguous Invasion

Peritoneal carcinomatosis is not uncommon, as at least in advanced stages of disease, 85% have some peritoneal involvement. Laparoscopy can help in the diagnosis as well as peritoneal cytology, which will be positive in 20 to 30 % of the patients who have no liver nor peritoneal metastases (Del Castillo et al.).
Peritoneal involvement due to invasion and perforation of the ventrally overlying peritoneum is present in about one third of the patients at least at autopsy. This situation is hardly ever addressed in the literature, as treatment is always palliative and the outcome very poor.

As discussed before, the instauration of at least attempts or even trials for aggressive treatments of peritoneal carcinomatosis (PC) has led to new insights in this dreadful and previously considered a fatal clinical situation. The staging method proposed as landmarks for treatment evaluation by Gilly et al. and recently applied in a multicenter french study (see Chapter 3 table 3.3.).
This study collected 370 patients with a non-gynecological malignancy in the period 1995-1997 and reported many interesting demographic and anatomic data.
There were 58 cases of pancreatic cancers with PC, of whom 69% diagnosed at first presentation and 55% in stages III-IV. The mean age was 65.5 yrs (range 26-89).
In their ongoing and diligent effort to examine the influence on prognosis of the extent of retroperitoneal invasion, Japanese surgeons have set some anatomic staging rules. Their contribution to the treatment of pancreatic cancer is great, but the obtained results are, in fact, rather disappointing, in spite of the sometimes enthousiastic claims.
Nevertheless, the efforts of the oncology surgeons have paved the way to a more disciplined tactical approach of the surgeical method.

The Japan Pancreas Society has established a complex stage classification of pancreatic cancer, including General Rules for the stratification of the lymph node groups and various other pathology features (table 10.33).

The UICC subsequently proposed a similar classification, but there are several differences, troubling the communication between surgeons of different countries.
Nevertheless, data on contiguous invasion are rarely discussed. A series of 8 patients presenting with gastrointestinal bleeding due to invasion of neighbouring organs has been published by Lee et al. In five of the cases there was a duodenal invasion, in two in the colon (one invading and one metastasis) and in one in the stomach.

Table 10.33 - Cancer of the Pancreas
Classification of the Degree of Contiguous Invasion
Japanese Pancreas Society

Retroperitoneum	rpo : no invasion
	rpe: invasion of retropancreatic space
	rpi : invasion in organs
Lymph Vessels	ly0 : no invasion
	ly1 : minimal invasion
	ly2 : moderate invasion
	ly3 : severe invasion
Nervous Plexus	Plx-ne° : no plexus invasion
	Plx-ne+ : invasion of the plexus (')

(') the retropancreatic plexus is divided into two portions:
Plx.pc1 : from the right celiac ganglia to the upper median margin of the uncinate process,
Plxpc2 : extends from the superior mesenteriuc artery to the median margin of the uncinate process.

In a consecutive series of 121 cases of pancreatic carcinoma, Bonetti found at endoscopy, duodenal lesions in 20 patients or 17%. In an additional 18 cases referred for endoscopy only, duodenal invasion was found. They were predominantly in part I or II. The lesions were either atypical ulcerations (11), stenosis (8), both in 11 and a polypoid tumor in 11.

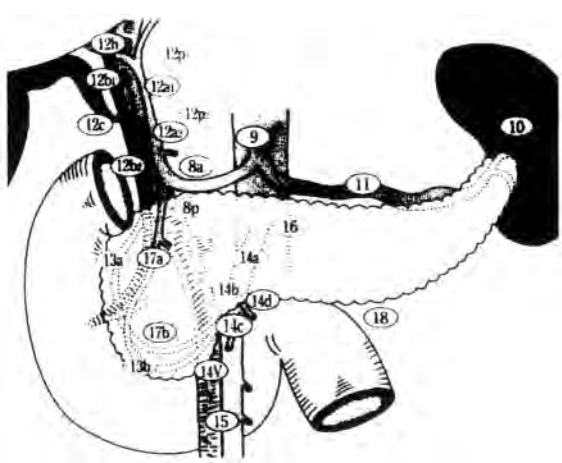

Fig.10.14 - Lymph Node Station numbers according to the Japanese System (for the legend see further)

Lymph Node Metastases

In their onngoing attempts to find any form of correlation between type and extent of invasion of the lymph nodes, Japanese surgeons have painstakingly codified and inventarized the different lymph nodes around and further from it. Their hope was to obtain better survival results and also to examine the

influence of the different stations on the prognosis (Fig.10.14 - 15, table 10.34).

A number of reports have produced lengthy tables on the incidence of involvement of each lymph node station or group. We will not duplicate these but try to summarize the results in respect of the so-called 'early pancreatic cancer, T1-T2'. It is obvious that in the more advanced cancers an increasing number of lymph nodes will be involved.

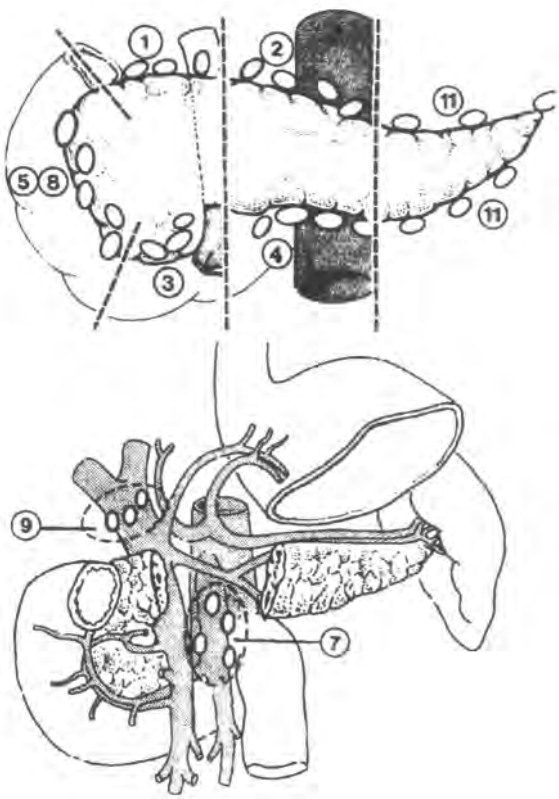

Fig.10.15 - Lymph Node Station numbers according to the UICC system

Lymph Node Station Numbers (JPS)

6	infrapyloric
7	along the left gastric artery
8	along the common hepatic artery
8a	anterosuperior node
8p	posterior nodes
9	around the celiac artery
10	at the splenic hilum
11	along the splenic artery
12	in the hepatoduodenal ligament
12h	hepatic hilum
12a1	superior along the hepatic artery
12a2	inferior nodes along the hepatic artery
12p1	superior nodes posterior to the portal vein
12p2	inferior nodes posterior to the portal vein
12b1	superior nodes along the bile duct
12b2	inferior nodes along the bile duct
12c	around the cystic duct
13	posterior surface of the head of the pancreas
13a	superior nodes
13b	inferior nodes
14	at the root of the mesentery
14a	at the origin of superior mesentery artery
14b	at origin of inferior pancreaticoduodenal artery
14c	at the origin of the middle colic artery
14d	along the first jejunal branch
14V	along the superior mesenteric vein
15	along the middle colic vessels
16	around the abdominal aorta
16a1	around the aortic hiatus of the diaphragm
16a2	around the aorta from superior margin of celiac trunk to the inferior margin of left renal vein
16bl	around the abdominal aorta from the inferior margin of the left renal vein to the superior margin of the inferior mesentery artery
17	on the anterior surface of the head of the pancreas
17a	superior nodes
17b	inferior nodes
18	along the inferior margin of the body and tail

UICC System

1	Superior to the head
2	superior to the body
3	inferior to the head
4	inferior to the body
5	anterior to the pancreaticoduodenal
6	anterior to the pyloric
7	posterior to the proximal artery
8	posterior to the pancreaticoduodenal
9	posterior, at the common bile duct
10	at hilum of the spleen
11	at tail of the pancreas

In the Japanese system, the stations are also grouped according to the progressive involvement, like in a stepwise fashion. Here too, there are discrepancies with the UICC system, but only the Japanese system is reproduced here.

Table 10.34 - Cancer of the Pancreas
Lymph Node Grouping (JPS)

Carcinoma of the Head of the Pancreas
Group1: 6,8a,8p,12a2,12p2;13a,13b,14b,14c,14d,14V, 17a,17b.
Group2: 9,11,12a1,12p1,12b1,14a,15,16a2,16b1,18
Group3: 1,2,3,4,5,7,10,12h,16a1,16b2 (')

Carcinoma of the Body and Tail of the Pancreas
Group1: 8a,8p,9,10,11,18
Group2: 7,12a2,12p2,12b2,13a,14b,14a,14c,14d,14V, 15,16a2,16b1,17a,17b
Group3: 1,2,3,4,5,6,12h,12a1,12p1,12b1,12c, 16a1,16b2
(') see chapter on stomach cancer

It would appear that the first station to be invaded is the inferior head group 3 (UICC) for cancer within the head, but micrometastases will already be present in the para-aortic group 7 (UICC).

Data of the lymphatic spread observed at autopsy were provided by Lisa et al. in respect of 104 cases. The peripancreatic nodes were involved in 42%, with a large majority at the head. Extension to the aortic,

mesenteric and retroperitoneal nodes occurred only in 14%. At the mediastinum and tracheobronchial nodes, the same amount was noted (14%), while there were cervical nodes in 7%.

Downward spread within the retroperitoneal space has been documented in a number of cases, but has apparently received less attention.

Distant Metastases

Compared with other gastrointestinal tumors, reports on distant metastases from cancer of the pancreas are less frequent. Except for the autopsy data already discussed and which confirm the low incidence, only case reports are at hand, a few of them involving revealing metastases.

Pulmonary Metastases

Pulmonary metastases are not uncommon according to some authors, but dedicated reports are scarce. In the autopsy reports, they amount to about 50%. Multiple cavitating metastases have been reported by Bunker et al.
In their autopsy series, Lisa et al. observed a difference in pulmonary metastases depending on the site of the tumor within the pancreas. When the head only was concerned, there were pulmonary metastases in 27%, while when the tail was involved, the figure was 52%. The pulmonary metastases observed ranged in size from miliary foci to solid tumors exceeding 7 cm in diameter. The most frequent pattern was bilateral multinodular dissemination. A solitary mass was found in 10%.
Based on the aspect of the chest X-ray in 12 patients, the diagnosis was first erroneously a bronchial cancer. The diagnosis of pancreatric cancer was only made at autopsy. In 8 of them the tumor, was located at the tail, confirming what was discussed above.

Cassière et al. have also addressed this problem and have reported on 10 patients in whom first a primary bronchial cancer was diagnosed, which turned out at autopsy to be a metastasis from a pancreatic carcinoma. This report confirms that pancreatic cancers can spread in the form of endobronchial metastases, a fact not reported in any other report.
Massive bronchorhea was the presenting symptom of lung metastases in a M39 (Lembo et al.).
Several cases have indeed been diagnosed first as bronchial cancers and were in fact type 1 presentation (Mishriki).
Recently a F71 was reported whose pancreatic cancer was revealed by sarcoidosis-like lung lesions (Mao et al.).
Pulmonary metastases mimicking a primary bronchiolo-alveolar carcinoma were reported in a M76, from an unknown pancreatic cancer, poning a serious problem in differential diagnosis (Steinke et al.).

Cutaneous Metastases

Reviewing the literature, Horino et al. found 49 cases of skin metastases reported, almost all in the Japanese literature. Multiple skin metastases were present in 36.4% of the cases, several involving the umbilicus, which was involved in 45.5% of all patients reported. Most were situated at the abdomen (see fig.7.3), and a few at the head and neck, of which two at the scalp. They concluded that skin metastases were liable to arise from tail-site lesions as there were several connected with peritoneal dissemination.
A revealing case at the umbilicus was reported by Shvili et al.
Nakanao et al. have reported on two patients with revealing metastases, one at the scalp and one with multiple sites. A plaque-like type was reported in a 63year-old woman as the first presentation of a pancreatic can-cer (Taniguchi et al.).

Liver Metastases

In a study specifically addressing liver metastases, Matsuno et al. showed a higher incidence of liver metastases in cancers located at the tail (47.3%) than those at the head (22.9%). More data are in table 10.35.

Table 10. 35 - Cancer of the Pancreas
Data on Liver Metastases (N=272)
Data of Matsuno et al.

Grade	Head N=179	Tail N=93	Total N=272
Overall	22.9%	47.3%	31.3%
Ho	77.0%	55.0%	69.0%
H1 (one lobe)	7.0	24.0	13.0
H2 (two lobes)	7.0	10.0	8.0
H3 (diffuse)	9.0	12.0	10.0

Relation between
Tumor Size, Lymph node and Degree of Metastases

	Ho	H1	H2	H3	Rate
T1(<2cm)	11	0	0	0	0%
T2(2-4cm)	65	7	3	3	16.6%
T3(4-6cm)	73	21	13	12	38.7%
T4(>6cm)	40	7	5	12	37.5%
NO	30	2	0	0	6.3%
N1	50	7	4	1	19.4
N2	56	11	9	12	36.4
N3	24	6	5	13	50.0
SO	30	1	1	0	6.3%
S1	30	6	4	4	31.8
S2	58	14	9	12	30.1
S3	42	6	5	11	34.4

So: no caps.inv.; S1: with invasion

The incidence of liver metastases correlates fairly precisely with the tumor size, the extent of lymph node metastases and the degree of capsular invasion.
In another study, Amikura et al. concluded that liver metastases were always present at diagnosis but were

mostly too small to be detected, highlighting the the likely uselessness of surgery.
DelCastillo has pointed to the fact that some of the liver metastases are in fact superficial metastases on the serosal surface and should be included under the number of peritoneal metastases. However, they give no data.

Muscle Metastases

A number of cases involving this metastatic site have been reported (table 10.36). The pathway is probably through the retroperitoneal space towards the lower extremity.
In a series of 9 patients presenting with muscular metastases, Folinais et al. mention a man of 43 presenting with paravertebral and cervical muscle infiltration by malignant cells. Only at autopsy, the diagnosis of a pancreatic carcinoma was obtained.

Table 10.36 - Cancer of the Pancreas
Muscle Metastases
Literature Review

Author	Pat	Site of Metastasis	Type
Belloir 1986	M75	Paravertebral muscles	Type 1
Larson 1988	M55	M.Gluteus Maximus Ri.	Type 2
Folinais 1988	M43	Paravertebral	Type 1
Wafflart 1996	M47	M.Vastus medius	Type 1
Perrin 1997	M67	M.Iliopsoas Le.	Type 1

Ophthalmic Metastases

They are rare in pancreatic cancer. A type 1 metastasis in the iris was reported by Barsky in 1978. The patient presented later with a testicular metastasis and the diagnosis of the primary was obtained only at autopsy.
Bilateral choroidal metastases occurred in a man of 45 a few weeks after the diagnosis of the primary. Ferry mentions one other case in his large survey of choroidal metastases.
A man of 38 presented with a typical orbital mass. The diagnosis was obtained only after an orbital exenteration. In the literature prior to 1960, two other cases were reported.
One case of metastasis in the optic nerve was reported in a woman (F61) 2 years after diagnosis and some time after developing diffuse bone metastases (Ring).
Recently, a woman (F66) was reported presenting with a choroidal metastasis and retinal dehiscence. She was found to have multiple lung metastases and at abdominal CT, a large tumor in the tail of the pancreas, later shown to be an adenocarcinoma (Cailliez-Tomasi et al.).

Head and Neck Metastases

We are aware of only two reports concerning tonsillar involvement and one on gingival metastases. Other concerned the epiglottis as revealing site and a gingival metastasis. An interesting fact is that in four patients it was the revealing metastasis of the pancreatic cancer (table 10.37).

Table 10.37 - Cancer of the Pancreas
Reported Cases of H&N metastases

Author	Patient	Site of Metastasis	Type
Oku 1980	M70	Larynx (Epiglottis)	Type 1
Feleppa 1981	M62	Tonsil	Type 3
Maor 1983	F59	Tonsil (bilateral)	Type 1
Stecher 1985	M46	Gingiva	Type 1
Freilich 1986	M62	Mandible	1 year
Vahatalo 2000	M65	Mandible	Type 1

Genito-Urinary Metastases

The few metastases reported in this region are tabulated below. They are very rare indeed, although we are aware of five testicular metastases (table 10.38).

Table 10.38 - Cancer of the Pancreas
Genito-Urinary Metastases

Author	Patient	Site of M	Type
Barsky 1978	M51	Testis Ri	Type 1
Werth 1982	M34	Testis Le.	Type 1
Algaba 1983	M44	Ri.Cord+Epidyd.	Type 1
Faysal 1983	M41	Ri.Epididymis	Type 1
Chiang 1992	F64	Urinary Bladder	Type 1
Stenner 1996	M41	Ureter Ri	Type 3
Stenner 1996	M79	Ureter Ri	Type 3
Dookeran 1997	M53	Ri.Epidydimis	Type 1
Dookeran 1997	M36	Testis Ri	Type 3
Richcoeur 1998	M57	Testis Le	Type 1
Rosser 1999	M58	Testis Le	Type 1
Sawa 2000	M73	Le.Spermatic Cord	Type 1

These metastases may be explained in terms of lymphatic or at least 'cellular' reflux within the retroperitoneal space. Retrograde venous or arterial embolism is also possible.
Metastases to the ovaries is a topic of its own. Diagnosis is probably difficult in view of the histological and clinical aspects. Young et al. have reported on 7 patients. They all presented with the clinical picture of an ovarian carcinoma. In five, the diagnosis of both tumors was simultaneous, but all had bilateral ovarian masses and also different peritoneal, mesenterial or other metastases. In two patients the pancreatic tumor was diagnosed before the ovarian tumors, respectively at 9 and 36 months.
Only a few other cases have been mentioned, but most are 'buried' in series concerning metastases in the ovary.

Bilateral ureteral obstruction was the first presentation in a case of extensive retroperitoneal metastases from a pancreatic head carcinoma found at laparotomy (Van Dyck et al.).

Urological involvement by pancreatic adenocarcinoma has been reported as including the adrenals, the kidneys, the ureters and the urinary bladder and must be

dsitinguished from true hematogenous metastases. At a latter stage, the urinary tract will be involved, but as in the case described above, can be the first sign. Involvement on the left side is predominant, with displacement of the kidney and progressive obstruction. Various though aspecific 'renal' symptomatology has been seen (review by Warden et al.).

Other Distant Metastases

Bone marrow metastases were investigated in a prospective study by Thorban et al. They examined 48 patients and found CK+ cells in 25 patients, or 52.1%. At follow-up, only one developed outright bone metastases, but 3 others developed liver metastases and 2 peritoneal recurrence. The problem of the significance of positive bone marrow is a well-known, as it is not always a positive sign of local metastatic development but more an expression of metastatic spread.

Obstruction of the right ventricular outflow tract was the presenting situation of a woman of 61; at autopsy, a metastatic pancreatic carcinoma was found (Labib et al.).

Bone metastases would seem to be rare. In a literature review of several reports spanning the years 1920 to 1957 and totalling 2,155 cases, only 110 patients were mentionned as having bone metastases, or 5.1% (Hatfield et al.). There was only 1% of bone metastases in those patients with pancreatic head locations and 4.7% for body and tail. In diffuse it accounted for 3.3%.
Site distribution within the skeleton has not been analyzed. The autopsy series mentioned above cites 12.5% in the spine.
Recently four patients with pancreatic cancer and bone metastases were described by Lyons et al. They remarked that the bone metastases were predominatly in the pelvic girdle.

Two unusual cases presenting with sudden hearing loss due to temporal bone metastases have been reported (Igarashi et al.; Ohira et al.). The pancreatic cancer was widespread in both cases but not diagnosed before the deafness. Another case was recently reported as presenting with sudden vertigo, headache and hearing impairment. CT disclosed multiple brain metastases and subarachnoidal hemorrhages. Death followed rapidly and at autopsy, a cancer of the tail of the pancreas was found (Wu et al.).

Of twelve patients with pancreatic cancer diagnosed with bone metastases, 5 or 41.6% had osteoblastic metastases, which does not correspond to the more usual reports of osteolytic metastases occurring in pancreas cancer.
Huber et al. have reported on a man M74 presenting with a pathological fracture at the distal end of the ulna. After different vagaries, laparotomy eventually disclosed a widespread pancreatic carcinoma.
In 1981, Compère et al. reported on a man (M73) presenting with a mass at the parotid region. A radiography disclosed a lytic destruction of the condyle of the mandibula. Biopsy showed a metastatic adenocarcinoma, apparently from a pancreatic carcinoma.

An 92year-old man was admitted to hospital with the diagnosis of a cerebrovascular incident and myocardial infarction. At autopsy, a pancreatic body carci-noma was found, with widespread abdominal meta-stases (Robinson et al.).
One case of thyroid metastases presenting with hyperthyroidism was reported by Eriksson et al. in a 54 year-old man. The diagnosis was made at autopsy, which also disclosed widespread abdominal metastases. The photograph of the patient also shows a fungating skin metastasis at the chin.
A fast evolving painful goiter was the revealing sign of a pancreatic cancer in a M45. A high CEA and Ca-19.9 indicated an abdominal cancer. Sonography detected a calcified tumor at the head of the pancreas, but at CT many retroperitoneal, liver and adrenal metastases were also present. Seven years earlier, skin nodules were excised and diagnosed as an adenocarcinoma of an unknown primary (Hsiao et al.).

Profuse hematuria in a woman aged 63 led to the diagnosis of numerous smoothly marginated filling defects within the renal parenchyma, with an irregular stenosis of the renal arteries. At autopsy a widespread pancreatic carcinoma was found, along with extensive retroperitoneal, hepatic, pulmonal and other metastases (Loughran et al.).
The same authors reported on a patient presenting with a symptomatology of hydronephrosis. At surgery, extensive retroperitoneal metastases from a pancreatic cancer were found.

At week 27 of gestation, a woman presented at emergency with low back pain. A large metastatic liver was found to contain adenocarcinoma. The patient died of renal failure after caesarean delivery of a healthy child. At autopsy, a widespread pancreatic carcinoma was discovered (Eltorky et al.).

It semms strange that no other cases have been reported, but there is probably not much interest in metastases of the pancreatic cancer, due to its diffuse and widespread involvement.

Causes of Death

In view of the tendency of pancreatic cancer to remain within the abdominal cavity, it is obvious that various situations will contribute to death of the patients, although several factors will be involved.
Amikura et al. have reported on the subject, in a study of the time-sequence of liver metastases (table 10.39).
These results conflict with the data of Matsuno et al. cited above, but it is not impossible that surgery has

had an impact on the figures.

Table 10.39 - Cancer of the Pancreas
Causes of Death (N=69)
Data of Amikura et al.1995

Operative Death	8.7%
Non-oncologic	8.7%
Unknown Causes	23.1%
Remaining 41 patients	
Recurrence with liver metastases	73.2%
Recurrence without liver metastases	26.8%
Cancer of Head after pancreatectomy (N=32)	
Recurrence with liver metastases	81.3%
Cancer of Body-tail after pancreatectomy (N=9)	
Recurrence with liver metastases	55.5%

Overall Lesson

Pancreatic carcinoma kills through abdominal spread, primarily retroperitoneally, but also through the high incidence of liver and peritoneal metastases. Distant metastases are relatively uncommon and the cause of death in a minority of cases.

METASTASES from ISLET CELL CARCINOMA

Islet cell carcinomas are very rare. Several endocrinologic types have beeni dentified, depending on the hormone secreted. Malignancy is defined by the histological or clinical presence of metastases. The incidence of malignancy varies according to the histologic types, from insulinoma with 15% to 25% to the other types where up to 75% have metastasized.
The best studied tumor group is the gastrinoma

Gastrinoma

About half (40-50%) of the gastrinomas are malignant, in the sense that they have visible metastases at diagnosis. Metastases mainly affect the lymph nodes and liver. The metastases can remain stable for many years. According to Weber et al., there is a definite correlation between the incidence of liver metastases and location of the tumor and their size. However, the percentage of lymph node metastases does not vary with the site of the primary (table 10.40).

Table 10.40 - Gastrinoma
Relationship of tumor size and incidence of metastases
Data of Weber 1995

Size	N	LyNo.	Liver	Any
less than 1.1 cm	45	20(42%)	2 (4%)	20(44%)
1.1 - 2.9 cm	32	10(31%)	9(28%)	16/50%)
more than 2.9 cm	41	16(41%)	25(61%)	39(90%)

It will be evident that while size does not affect the rate of lymph node metastases, there is a clear proportional increase of liver metastases with the size of the tumor. Table 10.39 indicates that

- the rate of lymph node metastases does not differ between duodenum and pancreas;
- the rate of liver metastases is much higher for pancreas gastrinomas, but though it should be remembered that the mean size of pancreatic gastrinomas is much larger. As the size correlates with that for liver metastases, this must explain the higher amount of liver metastases in the group of pancreatic tumors (Weber et al.).

In his world literature review, however, Soga found a higher incidence of lymph node metastases in extrapancreatic G (73% vs 31%) and of liver metastases in extrapancreatic G (85% vs36%) (table 10.41).
The influence of MEN pathology on the incidence of liver metastases is shown in the following table (10.40) (Weber et al.).

In MEN-1 there are fewer liver metastases at presentation, but they occur slighthy more frequent, although not to any significant extent during the follow-up (table 10.42). The reason is not clear.
Concerning liver metastases, Weber et al. demonstrated a significant difference in gender, in time lapse between onset and diagnosis and in the secretin level at diagnosis in the appearance of liver metastases (table 10.43). Are there different types of gastrinoma?

Table 10.41 - Gastrinoma
Relationship between location of the primary and the incidence of metastases
Data of Weber 1995

Site	N	LyNo	Liver	Any
Pancreas	42	20(47.6%)	22(52.4%)	30(71.4%)
Duodenum	41	20(48.7%)	2 (4.8%)	22(53.6%)
Panc+Duod	7	5(71.4%)	2 (28.5%)	6 (85.7%)
No Primary	47	24(51%)	4(8.5%)	N.G.
All	90	45(50%)	26(28.8%)	57(63.3%)

Data of Soga, world literature, 1999

	Pancreatic(N=218)	Extra (N=63)
Lymph nodes	31.2%	73.3%
Liver	84.9%	36.2%
Mesent.Perit.	8.6%	0
Bone	4.3%	3.3%
Lung	2.2%	3.3%

Table 10.42 -Gastrinoma
Influence of MEN-pathology on metastasis

	N	With liver M.	In F.U.
MEN-I	34	2 (5.8%)	9%
Sporadic	151	34 (22.5%)	5%
All	185	P=0.03	P=0.39

Other Metastases

A few reports have appeared of patients with bone metastases. They are consistently multifocal and often

Table 10.43 - Gastrinomas: Characteristics of Patients with or without Liver Metastases
Data of Weber et al. 1995

Features	No Hepatic Metastases	Liver Metastases during follow-up	Liver Metastases at presentation
N	140	9	36
Mean Age	54 ± 1 yr	51.5 ± 3 yr	51 ± 1 yr
Gender (M/F)	95/45 (°)	3/6 (°)	12/24 (°)
MEN-1 present	21%	33%	6%
Time Onset-Diagnosis	5.9 ± 0.5 yr (°)	2.4 ± 0.2 yr (°)	2.8 ± 0.4 yr (°)
Serum Gastrin (pg/mL)	1711 ± 30 (°)	2900 ± 220 (°)	5945 ± 1500 (°)
Secretin Increase(')	3194 ± 615	3024 ± 232	5691 ± 847
Basal Acid Output(mEq/h)	44 ± 2	55 ± 5	43 ± 2
Maximal Acid Output	62 ± 2	78 ± 6	53 ± 2

('): increase in level after secretin injection, over the average pretreatment value
(°): significantly different ($p<0.0001$) from value for patients who had hepatic metastases at the initial presentation or developed metastases with time

Table 10.44. - Metastases from Gastrinoma
Series of Vasseur (N=59, 1996)

39% with positive lymph nodes
39% with liver metastases (synchr. & metachron.)
In 59 patients the figures were:

Bones	6 or 10%
Lungs-pleura	1
Mediastinum	4 or 6%
Brain	1
Kidney	1
Myocardium	1
Retroorbitary	1

symptomatic. Bone metastases constitute 12.5% of the bone metastases in gastrinoma patients (table 10.43). The spine is always affected. They are relatively common in advanced gastrinomas, so that bone scans should be performed routinely in these cases (Barton). Roent-genograms show either lysis or sclerosis (Durieux).
The detection of bone metastases is of importance for decisions on the treatment. The problem of detection and imaging of these metastases was addressed by Gibril et al. They initially found that bone metastases were only present in patients with liver metastases.
This delimits the groups at risk to be studied further. Initial metastases were primarily in the spine or sacrum (75%) followed by pelvis or sacroiliac joints (38%). During the later course of the disease, spinal metastases accounted for 88%, ribs in 62%, shoulder in 62%, pelvis and sacroiliac joints in 50%, scapula 38% and femoral heads in 28%. Contrary to what is currently believed to happen with carcinoids, peritoneal dissemination was never observed.

Glucagonomas

Distant metastases occur in about 80% of the patients. The site of the metastases is usually the liver, but other sites are also involved (table 10.45).
A peculiar case was reported by Staren et al. A 36year-old man presented with signs of spinal cord compression and two subcutaneous tumors over the sternum. There were diffuse bone metastases, and CT showed a tumor in the head of the pancreas. Biopsy of the tumor in the vertebra showed a poorly differentiated carcinoma. Nearly two years later, at laparotomy for obstruction, a biopsy of the pancreas disclosed a glucagonoma. Elevated serum glucagon at 1490pg/ml. confirmed the diagnosis, but it is remarkable that the patient had no skin symptoms at any time. Patient later later cervical nodes and a cerebellar mass. According to the authors, up to then only four other cases of bony metastases had been reported.

Table 10.45 - Glucagonoma
Site of metastases

	Stacpoole N=84		Wermers N=69
Liver	43%		98%
Adjacent Node	14		38
Adjacent vessel	3.6		--
Vertebrae	2.4	(bone)	22
Lung	--		7
Mesentery	(1)		(1)
Adrenal	(1)		(2)
Spleen	(1)		(1)
Duodenum	(1)		--
Chest wall	--		(1)

Somatostatinomas

Malignancy occurs in about 70% of the cases. Metastases are most frequently in the lymph nodes or liver. The paraduodenal nodes are involved in the majority of cases. Other reported sites include peritoneum, skin, bone, kidney, ovary, adrenal and thyroid gland.
Recently, one case was reported with brain metastases (Abe). These authors remarked that the serum level of somatostatin is not of any significance for the diagnosis of metastases, at least in their case of cerebral metastases.

In his literature review, Soga disclosed more liver metastases in pancreatic (40% vs 11%) and more lymph node metastases in duodenal S. (35% vs 25%). No bone metastases were reported in duodenal S.

Other Islet Cell Cancers

A woman (F73) presented with recent pain in the left eye, with loss of visual acuity. Multiple choroidal elevations were visible in both eyes and she was diagnosed as having metastases from an unknown tumor in spite of extensive studies, although there was an unclear and progressive lung shadow. She died one year later and at autopsy a large 'islet-cell' carcinoma was found, also with metastases in the peritoneum, liver, lungs, kidneys, thyroid, brain and particularly the pituitary. More precise details about the nature of the tumor were not given (Solomon et al. 1974).

A woman (F52) presented with acromegaly, diabetes insipidus and visual impairment. Circulating levels of growth hormone and of somatomedin were elevated. The patient soon became cachectic and died. At autopsy, a large malignant primary was found in the pancreas, with metastases in the pituitary, the brain including the cerebellum, the lung, the liver and adrenal glands (Genka et al.).

Known as having a chemotherapy-treated islet cell cancer and liver and bone metastases, a woman (F53) presented with severe headache. A swollen right orbital ridge, proptosis, diplopia and visual troubles were found at MRI to be caused by a mass within the orbit. Biospy confirmed its metastatic nature (Gotwald et al.).

METASTASES from ADRENOCORTICAL CARCINOMA

Adrenocortical carcinoma is a very insidious tumor and except for the hormonally functioning tumors, is usually diagnosed at a late stage. In recent years, some can-cers have been diagnosed earlier, due to incidental finding as incidentalomas.
Hidden in the retroperitoneal space, the tumor will grow slowly and invade the neighbouring structures. Probably because of the rich vascularisation of the adrenal, access to the systemic circulation is early and the source of distant metastases, present at diagnosis in 50% to 70% of the patients. Literature or case-reports on revealing metastases are almost absent.

Spread - Metastases

The adrenal tumor first expands locally within the capsule, later through it, and it then invades the perirenal fat. The tumor can reach rather large dimensions because of the slow growth and the absence of any symptom. It will eventually invade neighbouring structures and organs.

Lymphatic Spread

Metastases will occur in the regional paraaortic lymph nodes, extending further into the abdominal nodes, either in the mediastinal and supraclavicular lymph nodes (fig. 10.16).

Distant metastases

About 50% of the patients (in some reports up to 80%), have distant metastases at diagnosis. The aggressiveness of the adrenal carcinoma is characterized by its number of distant metastases in many organs (table 10.46). The lungs and the liver are the most frequently involved, but almost every other organ can be involved, even as first sign, revealing a silent adrenocortical carcinoma.
Apart from the organs mentioned, metastases have been reported in the heart, the pericard, the breast, the diaphragm, palate, bowel, small bowel, colon, orbit, pleura and skin.
The data in table 10.44 show the high incidence of lung metastases. Within the abdomen, involvement of the peritoneum and retroperitoneum is common, while the liver has a high incidence. The involvement of the kidney is variably reported as being between 5 and 20%.
An early report on 175 cases by Hutter mentions distant lymph nodes in 10%, in some cases with mediastinal and thoracic duct involvement. This is also stressed in the report of Hajjar et al., who quote six cases where a distant non-regional lymph node was the first sign of an adrenal cancer, either cervical, supraclavicular, axillary or inguinal. They also mention bone metastasis in the extremities (no details), in the skull and in the clavicle.
While Hajjar et al. mentioned one case of metastases in the diaphragm, several more were included in the report of Cohn et al. They also observed one metastasis in the palate. Recurrences after surgery were seen twice in the stomach. Of 30 patients with metastasis in the series of Bodie et al, three were at the diaphragm and one at the psoas muscle.

Mediastinal involvement (5%) was stressed in the report of Venkatesh et al., as well as in the contralateral adrenal (10%). In the report of Luton et al. on 88 patients we found one case with metastases in the orbit and one in the skin. Pommier et al. also mention 10% in the diaphragm and one case in the palate.

Kwauk et al. reported on 24 cases from the same institution, in whom pulmonary metastases were present at diagnosis. Only in seven patients the metastases were unilateral. Only three only could be operated on. Multiple metastases elsewhere, pleural effusion, mediastinal nodal disease implicated inoperability of the primary or of the lung metastases as well.

A peritoneal carcinomatosis after laparoscopic resection of a malignant adrenal aldosteronoma has been reported by Deckers et al.
A number of cutaneous metastases were mentioned in the above-cited series.

Table 10.46 - Cancer of the Adrenal
Overview of distant metastases as reported in different literature series

Organ	Hajjar MDA N=30 1975(*)	King NCI N=49 1979(°)	Nader MDA N=77(') 1983	Cohn MSK N=47 1986(°)	Venkatesh MDA N=110 1989	Bodie Cleveland N=30(§) 1989	Luton France N=105 1990	Pommier MSK N=53(§) 1992
Abdomen								
Ly Nodes Reg.	5	--	19(32%)	24%	23(26.1%)	10(33%)	--	25/53
Liver	16(53%)	27(93%)	39(65%)	42%	56(63.7%)	15(50%)	43/88	47/53
Peritoneum	3	23(79%)	20(33%)	--	23(26.1%)	11(36%)	--	9/53
Retroperiton.	3	13(45%)	--	--	--	--	--	--
Pancreas	3	5	4	12%	4(4.5%)	2(6.7%)	4/88	--
Spleen	3	2	4	6%	4(4.5%)	--	1/88	--
Mesentery	2	--	--	--	--	1(3.3%)	--	--
Kidney	20	3	2(3.3%)	--	3(3.4%)	8(26%)	--	--
Other adrenal	3	1	8	---	8(9.1%)	--	1/88	--
Ovary	1	--	2	--	--	--	1/88	--
Supradiaphragmatic								
Lungs	18(60%)	23(79%)	43(72%)	45%	63(71.6%)	14(47%)	43/88	43/53
LyNodes other	9	8(28%)	--		5(5.7%)	--	--	--
Bones	10	7	14(23%)	15%	18(20.5%)	4(13%)	13/88	15/53
Brain	3	3	3(5%)	--	4(4.5%)	2(7%)	2/88	--

(*) summarized; (°): autopsy; ('): 60 with metastases; (*) 33 patients stage IV; (§) stage IV-patient.
MDA: MD Anderson Hospital, Houston, Texas; MSK: Memorial Sloan Kettering, New York;
NCI: National Cancer Institute

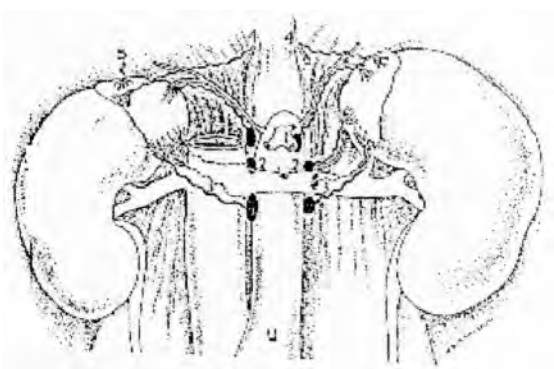

Fig.10.16- Lymph drainage from the adrenals. (1) along the art.suprarenalis superior, (2) arteria suprarenalis media, (3) anterior and posterior to the vena renalis inferior, (4) lymphatics through the diaphragm to the mediastinal nodes, (5) lymphatics to the liver. (from Ackerman & DelRegato, with permission)

They are, however, very rare: less than 1%. Hajjar et al. and Luton et al. each mention one case with several cutaneous metastases. In a large review of cutaneous metastases, Gates et al. found 3 cases from adrenal cancer.

A revealing case of metastases to the cheek was reported by Roudier et al. in a man of 61year. Biopsy could only determine that this was a malignancy. An abdominal CT disclosed a large (9 x 8cm) tumor in the left adrenal, together with some lung metastases. The identity of the adrenal malignancy was obtained at fine needle biopsy and was identical to the skin biopsy.

We are aware of two cases with cardiac metastases. Both were at the wall of the right atrium, one at the interatrial septum (Bilge et al.). The patient died of complications including Budd-Chiari syndrome. In the other patient, the metastasis was at the posterior wall. The latter was only found at autopsy after the man (M63) presented in shock at emergency. He was found to also have many other metastases from an adrenal cancer operated on 3 years previously (Dickens et al.).

Other data on adrenal metastases are not at hand in the literature.

Tumor Thrombus in the Inferior Vena Cava

A particular problem encountered in some cases is the presence of a tumor thrombus within the vena cava extending up to the right heart. Figueroa recently reported six cases and found a small number in the literature. A more extensive literature review has been provided by Hedican et al., who found 26 other cases and added 3 from their files. Data are in table 10.47. The large majority are right-sided adrenal tumors. This can be explained in terms of the shorter adrenal vein at the right.

The thrombus consists of an independently vascularized collection of malignant cells embedded within clotting elements. The primary tumors are larger, with a mean size of 10cm.

There is a significant preponderance of female patients, nearly four times the male number.

Striking is the high proportion of functional tumors, suggesting the hypothesis of an influence of the hormonal products in the vein. Some are only intrahepatic (level II) but many are intra-atrial (level III). MRI is the imaging method of choice; less risky than venography.

Since the review by Hedican, Figueroa et al. have reported on six other patients, of whom 5 were on the right. Four of them were female patients.

More than two years after diagnosis in a poor surgical candidate (F83), she presented with a dramatic increased left tumor, with invasion in all neighbouring organs, with a large thrombus in the splenic artery (Stein et al.).

Table 10.47 - AdrenoCortical Carcinoma
Data on Patients with caval thrombus
Literature Review by Hedican et al.1997

Pathology	Right 83%		
	M/F ratio 1/3.8		
	Tumor Size mean 10.1 cm (6-20)		
	Thrombus Size 89% >9 cm length		
	Function/Nonfunction.women 16/6(')		
		men 6/0	
	Age: Women F: 37±16 NF 62±10		
	Men F: 33±14 NF none		
	All F: 36±16 NF 62±10		
Symptoms at presentation	Women	Men	
		N=23	N=6
Cushing's syndrome		30%	17%
Virilization/Feminization		13	0
Menstrual irregul.		22	0
Precocious Puberty		0	17
Abdominal mass		13	0
Abdominal pain		35	50
Ascites		13	33
Peripheral Edema		30	17
Dyspnea		9	0
Weight loss		9	0
Weight gain		4	0
Hypertension		0	2

(') One with unknown status
F: Functional, NF nonfunctional tumor.

Recently a 'giant' recurrent contralateral metastasis (or new primary?) was reported six years after resection of the first (Kunieda et al.) The patient (M52) had no other metastases.

Overall lesson

Adrenal cancer metastasizes early. This is probably a faulty impression, as the diagnosis is usually late, due to its silent evolution. Modern imaging methods allow earlier detection, though possibly incidentally. There are no data on their presentation.

Future reports should pay more attention to the presenting metastastatic sites.

METASTASES from MALIGNANT PHEOCHROMOCYTOMAS

Pheochromocytomas are a proliferation of paraganglion cells, labeled pheochromoblasts, either adrenal or extra-adrenal. The main biochemical function is the secretion of cathecholamines (adrenaline and NOR-adrenaline), which is responsible for the clinical syndrome.

About 10% of all pheochromocytomas are reported to be malignant. As is the rule in endocrine tumors, by definition, the pheochromocytoma will have metastasized. Metastases of pheochromocytomas have been reported in bone, liver, lungs and in the lymph nodes. Many authors state that this is underrated. Length of follow-up in most of the reports is usually rather short. There are no studies reporting data on the metastatic pattern.

Risk Factors for Malignancy

A large number of studies have addressed the matter of what fact are able to predict malignant behavior.

Two situations can be distinguished, as proposed by Mornex et al.:

1. About half of the pheochromocytomas are apparently benign when first discovered. They recur later, an average of 7-8 years later, but the period can be as long as 22 years.
2. The other half of the patients have malignant signs right from the beginning.

In a small group of 20 malignant pheochromocytomas, Nativ et al. reported the following incidence:

lymph nodes	42%
liver	37%
bones	21%
lungs	16%

Reporting on 30 malignant P-patients, Shapiro et al. mention a majority of male patients (21/30), a mean age of 32years (10-57 yrs) with 11 under the age of 18 years. The mean interval before the diagnosis of metastases was 9.18 yrs (0-33yrs). The primary was extra-adrenal in 13 cases: pararenal in 4, bladder in 21, para-aortic in 2, para-adrenal, pancreatic, left atrial and abdominal in one and in one it was widespread.

Proye et al. state that some clinical signs are more frequent in malignancy:

Flush	(27% vs. 6%)
Erythrocyte SR	(46% vs. 10%)
Dry cough	(15% vs 2%)

Flush is related to the secretion of other hormonal products. The dry cough may have the same cause, though this is lesser clear. It disappears after resection of the tumor(s).

Some authors have tried to correlate histo-cytological features with the malignancy outcome of the pheochromocytomas.

Cellular Differences

An extensive study providing a score system was done by Linnoila et al. We thought it worthwhile summarizing.

Features noted more frequently in malignant tumors were
- male predominance (74%)
- extra-adrenal location
- larger tumor weight: mean 383g vs 73g
- confluent tumor necrosis
- presence of vascular invasion and/or extensive local invasion

Four histological parameters were the most predictive:
- extra-adrenal location
- coarse nodularity of primary
- confluent tumor necrosis
- absence of hyaline globules

Most malignant paragangliomas had two or three of these features, while 89% of the benign had only one. More than 70% of the tumors could be correctly classified on the basis of the four factors indicated (table 10.48).

Table10.48 - Paragangliomas
Prediction of Malignancy (Linnoila et al.)

Step 1	- Score 116 if extraadrenal
Step 2	- Score 161 if coarsely nodular growth
Step 3	- Score 158 if tumor necrosis
Step 4	- Score -156 if cytoplasmic hyaline globules
Step 5	- Sum the scores
Step 6	: if sum equals or exceeds 100, the tumor is malignant

Malignant pheochromocytomas have been divided on an histocytology basis into four types by Kimura et Sasno:
1. Spindle-shaped cell type
2. Small round cell type,
3. Pseudo-rosette forming,
4. Mixed neuro-endocrine-neural type.

They showed also that malignant P. are composed of significantly smaller cells with a higher nuclear/cytoplasmic ratio compared to benign tumors.
Similar predictors for malignancy were outlined by Pattarino et al. (table 10.49).

In view of the cellular dedifferentiation the production of beta-hydroxylase, which catalyzes the transformation of dopamine to norepinephrine, it has been proposed that the excretion of dopamine or of its metabolites could suggest the diagnosis of malignancy. Schlumberger et al. have presented a series of 20 patients, stressing many interesting features (table 10.50).

Table 10.49 - Pheochromocytoma
Predictors of Malignancy (Pattarino et al.)

Young age of onset	
Female patient	
Extra-adrenal tumors (table 8.1)	
Familial lesions	
Tumors associated with other endocrine or neoplastic disorder	
Large tumors (>200 g.)	
High mitotic activity (>5/10 HPF) (Brückner)	
Loss of S-100 protein-positive sustentacular cells (Brückner)	
Are apparently not associated with malignancy	
Bilateral involvement	
Urinary catecholamines, except dopamine	
Mitosis, giant cells and nuclear pleomorphism (Mornex et al.)	

Table 10.50 - Malignant Pheochromocytomas
Clinical Features (N=20)
Data of Schlumberger et al. 1992

Diagnosis of Metastases was done	
at first presentation	11
at follow-up (10-30 mo)	7
at follow-up (9-28 yrs)	2
Symptoms of Metastases	
Catecholamine effects	88%
constant hypertension	14/20
paroxysmal hypertension	10/20
palpitations	13/20
sweating	14/20
hyperglycemia	6/20
constipation	9/20
Local Tumor effects	
bone pain (metastases)	7/20
abdominal pain	2/20
weight loss	7/20
Asymptomatic	1/20

Site of Metastases

There was no correlation between biochemical results and the tumor load. The site of the metastases was not tabulated but they were mostly in lung, liver, bone and lymph nodes. Bone marrow metastases were frequent. Fourteen patients died and their median survival was 16 months from the diagnosis of metastases. Response to systemic treatments, either radionuclides or chemotherapy, was poor.
The best-studied metastatic site is bone.
According to Lynn et al., 38 patients out of 56 metastatic (68%) pheochromocytomas had bone metastases. Their anatomical distribution is given in fig. 8.15. The average interval from diagnosis of the primary was 6.5 years (range 0-20 years).

Bone metastases are the major metastatic site in malignant pheochromocytoma and are usually located within the axial skeleton, but metastases in the clavicle, sternum, femur and humerus have also been observed. Some patients have widespread disease involving bone associated with pulmonary metastases,

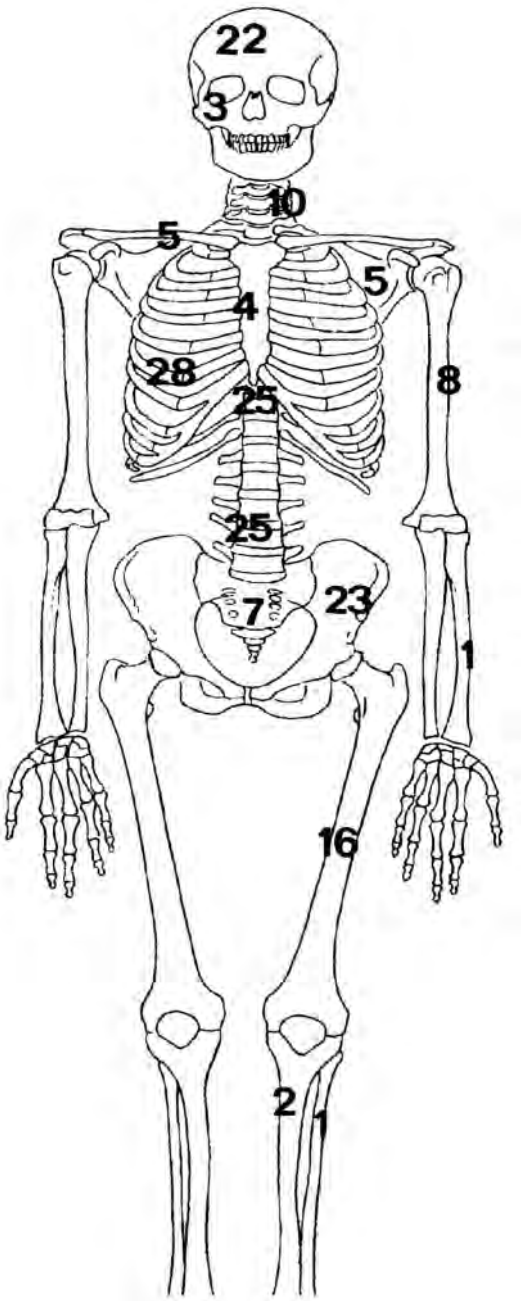

Fig.10.17 - Distribution of bone metastases in 38 patients with malignant pheochromocytomas. Data of Lynn 1986.

massive retroperitoneal nodes and liver. Some have only been reported in small series treated with radioactive nuclides and/or chemotherapy.

Spinal metastases have evolved in some patients to cord compression (table 10.51), associated with many other metastatic bone sites.

Pulmonary metastases usually present as multiple parenchymal nodules. They are peripheral, multiple, variable in size and sharply outlined. Mediastinal lymph node metastases are not rare. Lymphangitic and pleural metastases have not been reported. One case of endobronchial metastases was recently described by Sandur et al.

Table 10. 51 - Malignant Pheochromocytomas Patients with Spinal Cord Compression

Author	Pat	Primary	Level	Interv
Scott 1982	M53	no data	T4	simult
Mertens 1993	M23	Extra Adr.	T9	6 yrs
Tato 1997	F16	Ri.Adren.	T6	6 mo
Mateos 2000	M35	Extra Adr.	T5	3 yrs
Hamilton 2000	M16	Extra Adr.	T6	1 yr
Hamilton 2000	M17	Extra Adr.	Multi	3 mo

One specific complication, though infrequently reported involves metastatic thrombosis in the vena cava inferior. It is analogous to adrenal carcinoma but much less frequent (table 10.52). Most were simultaneous presentations.

Table 10. 52 - Malignant Pheochromocytomas Cases with Intracaval Thrombotic Extension

Author	Patient	Primary	Thrombus
Rote 1977	M52	Le.Adren.	Simult. to RA
Scott 1982	M31	Extra Adr.	Infiltration in VC
Dicke 1987	F39	Ri.Adren.	Small thrombus
Fisher 1988	M66	Ri.Adren.	Small
Lau 1997	M18	Le.Adren.	(4 yrs) thrombus

One patient (M56) was reported by Raghavan et al. as presenting with clinical signs of cerebral thromboembolization, caused by multiple mural thrombi in the upper aorta, metastatic from an unknown pheochromocytoma disclosed at autopsy. Other type 1 presentations have also been reported, mainly in the series of Scott et al., one (F54) with a pathological fracture in a clavicle and two patients with skin nodules over the scalp (M53 and M53).

Indicators of Malignancy

Table 10.53 shows that half of the malignant pheochromocytomas are extra-adrenal and a large number of these are malignant.

Based on 33 non-consecutive patients, selected for a reliable long-term follow-up, Clarke et al. were able to list a number of indicative features associated with malignancy (table 10.54). Only two histochemical reactions were indicators, and at multivariate analysis still MIB-1 was significantly associated with malignancy. MIB-1 at a cut-off value of more than 3% yielded a specificity of 100% and a sensitivity of 50% in predicting malignancy.

Additional features and data were recently published by Johns et al. Age, gender, symptoms and diagnostic delay were not significant in the correlation with malignancy, nor the associated syndromes. Twenty-four hour urinary dopamine concentration, persistence of hypertension, extra-adrenal location and tumor

weight were the significant findings (table 10.55).

Table 10.53 - Malignancy according to site of primary Pheochromocytoma (N=587) Literature review by Mornex

	Benign	Malignant	All
Adrenal	439 (92.6%)‘	35 (7.4%)	474
Extraadrenal	74 (65.4%)°	39 (34.5%)	113
Total	513 (87.4%)“	74 (12.6%	587

(‘) of adrenal P.; (°) of extraadrenal P.,(“) of all P.

Table10.54 - Pheochromocytoma Prognostic markers for malignity (N=33, 23 benign, 10 malignant) (Clarke et al. 1998)

Parameter	Benign	Malignant	P
MIB-1 stain mean%	1	5	.0009
S-100 staining	strong	low	.02
Gender M/F	10/13	9/1	.008
Extra-adrenal	9%	40%	.03
Neurofibromatosis	5	0	.04
Age at resection	49-yr	38-yr	.05
Tumor Weight (g)	124	481	.05

Table 10.55 - Pheochromocytoma Factors predicting malignancy from data by Johns et al. 1999

		P
24hr-urine	Dopamine>5000n.mol/24hr	<0.0001
Location	Extra-adrenal site	= 0.03
Tumor	Weight > 80 g.	<0.0001
	Tum.dopamin > 120 n.mol/g	= 0.003
	DNA tetra- and aneuploidy	
Blood pressure	post-operative persistence	=0.001

METASTASES from PRIMARY PERITONEAL MALIGNANCIES

The peritoneum is a rare site for primary cancers. The most frequent are the mesothelioma and serous papillary carcinoma of the peritoneum, sometimes reported as a primary adenocarcinoma.

The majority are malignant through their local spread within the peritoneal cavity leading to intestinal problems. Differential diagnosis with the more frequent secondary cancers is mandatory, but is mainly a task for the pathologist after careful surgery.

Peritoneal Mesothelioma

Reviewing the literature on peritoneal mesothelioma, Raptopoulos could retrieve reports on 83 autopsies and derive the incidence of distant metastases (table 10.56).

Clement et al. have reported on nine cases with ovarian metastases. They describe widespread peritoneal metastatic spread, probably encasing the ovaries.

Recently, a patient was reported presenting with pronounced respiratory symptoms. A M28 had dyspnea and dry cough. At chest imaging, he was found to have bilateral pleural effusion, pericardial fluid, multiple peripheral pulmonary nodules and cardiophrenic nodes. Further investigations disclosed an extensive peritoneal mass within the pelvis, which at biopsy was found to be a mesothelioma (Daskalogiannaki et al.).

Table 10.56 - Peritoneal Mesothelioma Incidence of Distant Metastases (N=83 autopsies) Data of Raptopoulos

Liver	44%	Adrenal	5%
Lymph nodes	33	Heart	5
Pleura	33	Lung	27

Other (bone, brain, spleen) : unknown

Table 10.57 - Peritoneal Malignancies Cases with Distant Metastases reported

Author	Patient	Site of Metastasis	Interval
Peritoneal Mesothelioma			
Kwee 1982	F66	Umbilicus	Reveal
Ordonez 1983	M54	Widespread skin	3 mo
Chen 1991	F54	Umbilicus	Reveal
Serous Papillary Carcinoma			
Miyaishi 1994	F61	Mediast.Pleura	14 mo
Eltabbakh 1997	F42	Liver, Brain (mult)	3 mo
Shmueli 2001	M53	SCnode as first Autopsy ‘everywhere’	--
Peritoneal ‘Carcinoma’			
Nalesnik 1999	F62	Brain Le.Parietal	15 mo

Serous Papillary Carcinoma

Now currently diagnosed and named ‘ovarian-like’ carcinoma, this cancer evolves like a metastasized ovarian carcinoma. They occur almost exclusively in female patients, male cases having been reported only twice (Shmueli etal.). Specific reports on distant metastases are rare however. Other particular case-reports are shown in table 10.57.

References

Caution: References are given for documentary purposes. Not all have been reviewed or used in the redaction of the text. We do not claim completeness of data. The references are as much as possible grouped per subject heading. For some headings, only reports after 1979 are listed.

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11
METASTASES from CANCERS of the UROGENITAL TRACT

Cancer of the Kidney	Cancer of the Ovary
Wilms' RenalTumor	Ovarian Germ Cell Tumors
Malignant Tumors of the Ureter	Cancer of the Tuba
Cancer of the Urinary Bladder	Cancer of the Endometrium
Cancer of the Urachus	Cancer of the Myometrium
Cancer of the Prostate	Cancer of the Uterine Cervix
Cancer of the Testis	Cancer of the Vagina
Cancer of the Penis	Cancer of the Vulva
Cancer of the Urethra	Gestational Choriocarcinoma

METASTASES from RENAL CELL CARCINOMA

Renal cell carcinoma has, compared with other cancers, unusual features. It is the 'chameleon' of the cancers. Its behavior as far as metastatic spread is concerned, is indeed uncommon and this makes comparison with other cancers difficult. Hidden deep within the retroperitoneal space, tumors can develop into large masses, early in their evolution in connection with a rich vascular network. This will allow early spread of tumor cells, and ensuing metastasis can become manifest before the primary is found. This cancer can indeed present with metastasis first, before the primary provokes any symptom, and more than any other malignant tumor at any place or site within the body. This behavior causes diagnostic difficulties due to the masquerading aspect of the metastatic presentation.
Another aspect is that metastasis can occur at any site within the body, even many years or decades after the first treatment.

Metastatic Pattern at Autopsy

The high number of cases and the high rate of metastases at death have permitted an insight into the metastatic evolution or cascade.
The metastatic pattern of renal cell carcinoma has intensively been studied by a number of authors, all of whom have tried to find an orderly pattern.
Saitoh's study involved 1,451 cases (table11.l).
The data show the high frequency of pulmonary involvement, even as solitary metastases. In this group, 21% of the patients had also tumor emboli at any site, probably as cause of death. The high number of pulmonary metastases indicates its central place in the further spread.
In the group where more than one organ was involved, there are a high number of skeletal and liver metastases and also of other organs commonly not involved in other cancers.
In spite of its location in the retroperitoneal space, renal cancer rarely metastasizes in the organs situated in this space, such as the pancreas or ureter, while the other kidney is involved in 25% of the patients.
Analyzing his data further, Saitoh could distinguish 3 different patterns. A first with a linear increase of the number of organs involved, seen in patients with pulmonary and nodal metastases.

Table 11.1 - Renal Cell Carcinoma
Metastasis Distribution - Autopsy Data (N=1451)
Data of Saitoh

Site	One-Organ N=120	Total N=1293
Lymph nodes	12%	66%
AbdominoPelvic		
Liver	6%	41%
Adrenal ipsilateral	2	17
Adrenal contraleral	2	11
Peritoneum	2	9
Retroperitoneum	2	3
Pancreas	1	14
Bladder	1	2
Ureter	1	1
Kidney contralateral	0	23
Intestine	0	9
SupraDiaphragm - Systemic		
Lungs	32%	76%
Bones	9	42
Brain	7	11
Skin	2	7
Pleura	0	12
Heart	0	11
Diaphragm	0	7
Thyroid	0	5
Tumor Emboli	21	8

In a second group, the frequency of the metastases was low whith only 1 or 2 organs involved, but markedly increased when three or more organs were involved. This group concerned pancreatic, cardiac and intestinal metastases. The last group had an unchanged fre-

quency regardless of the number of organs involved, mainly brain metastases. There was about no difference in the metastatic distribution between nephrectomized and not-nephrectomized, except for contralateral kidney involvement and brain, where the surgically-)treated cases had a higher incidence.

Table 11.2 - Renal Cell Carcinoma
Metastasis Distribution - Autopsy Data (N=687)
Data of Weiss et al.

Site	Lung Yes N=239	Lung No N=109	Total 687
Pelvi-Abdominal			
Adrenals	41.0%	32.1%	19.4%
Kidney	27.2	16.5	12.1
Liver	52.3	33.9	23.6
SupraDiaphragmatic			
Brain	23.0	10.1	9.6
Lung	(100)	0	41.2
Myocardium	15.5	7.3	10.2
Thyroid	12.6	8.3	5.7
Systemic			
Skeleton	20.9	18.3	10.2
Skin	6.3	4.6	2.9
Others(')	45.6	35.8	21.5

(') see next table

The metastatic pattern was analyzed by Weiss et al. in 687 necropsies. Of these the diagnosis was made first at autopsy in 173. Metastases were absent in 295 and in 44 there were only lung metastases. The further results are in table 11.2. The organs rarely involved are in table 11.3.

Table 11.3 - Renal Cell Caracinoma
Organs not frequently Involved
Number according to Metastasis Group (Weiss et al.)

Site(')	Lung Yes N=239	Lung No N=109
Pelvi-Abdominal		
Stomach	10	0
Colon	4	0
Omentum	4	2
Peritoneum	22	12
Pancreas	18	12
Spleen	12	2
Gallbladder	4	0
Testis	4	1
SupraDiaphragmatic		
Diaphragm	7	1
Pericard	5	1

(') only sites with more than 2 patients listed

Pathways

After passage of the cells through the heart, the lungs are the first parenchyme encountered by tumor cells leaving a renal tumor. This is reflected in the data, showing a high rate of pulmonary involvement. Nevertheless, except in those without any metastases (43%), there are lung metastases in 44+239 = 42%. It was the site with the highest number of metastases. It can be inferred that at least in renal cancer, the lungs are the 'turntable', the first step in the metastatic cascade (Weiss et al.).

The inefficiency, however, of the metastatic process is confirmed by the fact that metastases are found in 109 or 16% of the patients (109/687), whereas other metastases are found in a lesser degree than in the patients having pulmonary metastases (table 11.2). This could be explained by other routes taken by the cells, such as the mesenteric and portal veins and porto-systemic shunts, which may be assumed to happen more frequently in left-sided cancers, as has been demonstrated in non-oncological liver diseases. There was no difference according to the location of renal tumors in the data of Weiss et al. The Batson pathway could be invoked for these 'aberrant' metastatic sites.

When the ranked incidence observed was divided arithmetically by the blood flow in mL/min., a good correlation could be obtained with the observed incidence, inferring that the metastatic involvement cannot be explained solely by the seed and soil theory (Weiss et al.).

Lymphatic Spread

The regional lymph nodes are the para-aortic and the paracaval nodes. The juxtaregional lymph nodes are the intrapelvic, the mediastinal and the supraclavicular nodes.

N0 : no evidence of lymph node involvement
N1 : Involvement of a single homolateral regional lymph node
N2 : Involvement of contralateral or bilateral or multiple regional lymph nodes
N3 : Involvement of fixed regional lymph nodes, assessable only at surgery.
N4 : Involvement of juxtaregional lymph nodes.

The incidence of involved nodes at different sites was also studied by Saitoh in 1,451 autopsies. Overall 66% of the patients had nodes involved at any site (table 11.4).

Table 11.4 - Renal Cell Carcinoma
Lymph nodeMetastases at Autopsy (N=1451)
according to Metastasis Group (Saitoh)

Site	Lung Yes N=239	Lung No N=109
Abdomen	30%	36%
Retroperitoneum	65	70
Mesentery	14	19
Inguinal	4	I
Mediastinal nodes	10	5
Tracheal nodes	70	23 (°)
Cervical nodes	9	8
Supraclavicular nodes	13	10
Axillary nodes	2	3

(°) significant at P<0.01

There is no difference between the two groups - lungs involved or not - as could be expected, because lymphatic dissemination does not follow systemic circulation. The high number of hilar nodes in cases of lung involvement is probably indicative of a secondary spread. In an autopsy series of 554 patients in whom the renal cell carcinoma was found only at autopsy, metastatic spread to any lymph node was found in 80 (14.4%) patients (Johnsen et al.). We have tabulated their data in table 11.5.

Table 11.5 - Renal Cell Carcinoma found at autopsy
Lymph node metastases (N=80)
Data of Johnsen et al.

Only para-aortic-paracaval	21 cases
with other sites involved as well	37
Total 21 + 37 = 58 or 73%	
Pericapsular growth	71/80
Mediastinal nodes present	52
Mediastinal only in 8	
Supraclavicular	28
Supraclavicular only in 1	
Axillary in	5
Axillary only in 1	
Inguinal	2

Only 5 of the 80 patients had only lymphatic involvement. In the literature, a small number of patients have occasionally been reported as showing only supraclavicular, mediastinal or even axillary nodes.

A rare occurrence is the lymphoma-like presentation of an unknown renal cancer, where lymph nodes are found in all clinically accessible node regions, and by further examination also abdominal and mediastinal. We personally remember two such cases.

Lymphadenectomy for renal cancer is different for the right and the left kidney.

For a left tumor, the para-, the pre- and retroaortal lymph nodes are to be removed from the renal pedicle to the bifurcation. For a right tumor, the para-, pre-, retro- and interaortocaval nodes must be dissected (Fig. 11.1). This should be compared with the dissection for testicular tumors.

Surgical data on lymph node involvement according to each station are, however, almost absent in the literature. As usually only 'operable' cases are resected with lymphadenectomy, it is understandable that the rate of involvement in surgical patients is rather low. Herrlinger et al. have provided data from 381 radical nephrectomies. Metastases were present in 29%. In stage I-II there are nodes as is to be inferred from the surgical results and the staging rules. The average number of nodes resected was 24.5 in complete dissection and 6.1 in the 'partial' group (table 11.6). Data for stage III and IV are of course not reported.

Table 11.6 - Renal Cell Carcinoma
Incidence of Involved Nodes at Surgery (N=381)
Data of Herrlinger et al.

	All (381)	Curative (M0)
Partial Dissect.	14% (170)	13% (157)
Complete Dissect.	23% (211)	22% (195)

Local Regional Spread

The anatomy of the renal fossa is such that after cancer cell have broken through the renal capsule, they will have the opportunity to invade the whole retroperitoneal space, as well as the different venous plexus located between both kidneys.

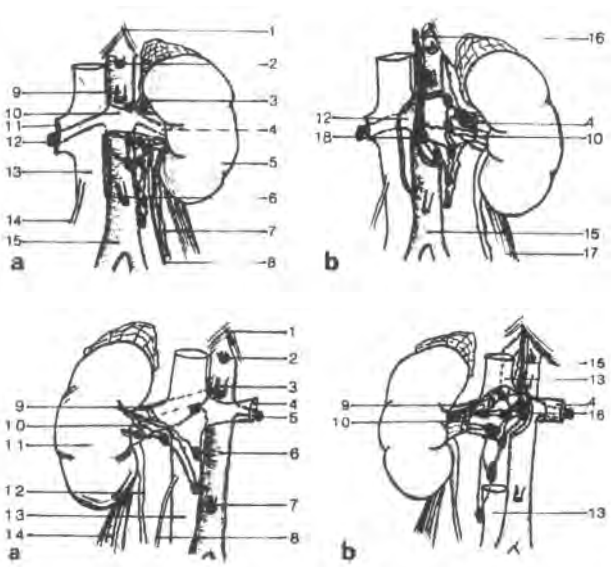

Fig. 3 a, b. *Regional lymph nodes of the left kidney* (anterior (a) and posterior (b) aspect). *1,* Hiatus aorticus; *2,* Truncus coeliacus; *3,* V. suprarenalis; *4,* A. renalis sin.; *5,* V. renalis sin.; *6,* A. mesenterica inf.; *7,* Ureter sin.; *8,* V. spermatica/ovar. sin.; *9,* A. mesenterica sup.; *10,* V. renalis sin.; *11,* V. renalis dex.; *12,* A. renalis dex.; *13,* V. cava; *14,* V. sperm./ovar. dex.; *15,* Bifurcatio aortae; *16,* Ductus thoracicus; *17,* Musculus psoas; *18,* Cysterna chyli

Fig. 4 a, b. *Regional lymph nodes and lymph vessels of* the right kidney (anterior (a) and posterior (b) aspect). *1,* Hiatus aorticus; *2,* Truncus coeliacus; *3,* A. mesenterica sup.; *4,* A. renalis sin.; *5,* A. renalis dex.; *6,* Aorta; *7,* A. mesenterica inf.; *8,* V. sperm./ovar. dex.; *9,* A. renalis dex.; *10,* V. renalis dex.; *11,* ren. dex.; *12,* Ureter dex.; *13,* V. cava; *14,* Musculus psoas; *15,* Ductus thoracicus; *16,* Cysterna chyli

Fig. 11.1 - Regional lymph nodes of the right and left kidney (from Herrlinger et al., with permission)

A literature review by Ritchie shows that 23% had distant metastases at diagnosis. According to Schmiedt, 28% of the renal tumors had at diagnosis already invaded the perirenal fat, 70% had already broken through the renal capsule and between 20 to 40% had positive regional nodes. Tumor thrombi were present in the vena cava in about 10%, but up to 50% in the renal veins.

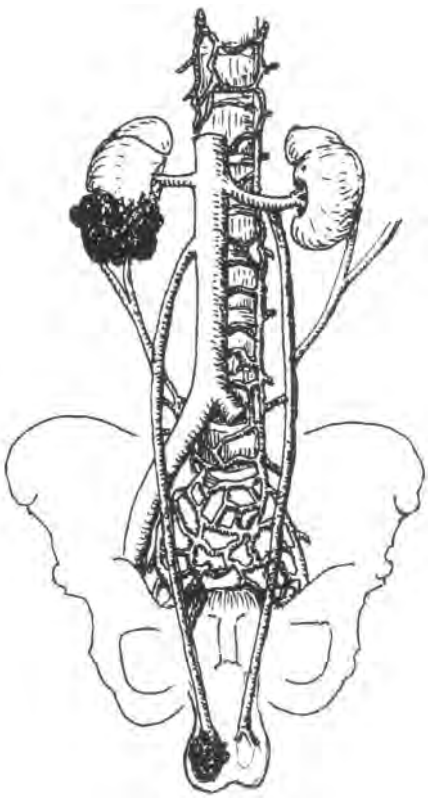

Fig. 11.2 - Diagramatic illustration of the local, regional and venous spread of a renal cell carcinoma

The complex relationship between perirenal tissue and the retroperitoneal venous plexuses will explain various 'uncommon' metastasis within the retroperitoneal space and pelvic metastases, in pelvic bone, urinary bladder and genitalia of both genders (fig. 11.2).

Distant Metastases

In view of the large number of sites involved by renal cell carcinoma, we thought it appropriate to divide the discussion on distant metastases in three parts, the abdomino-pelvic metastases, the supradiaphragmatic metastases and the systemic metastases.

Distant metastases must occur either by hematogenous way either secondary to the lymphatic drainage.

It is important ito have knowledge of the anatomy of the renal veins. Around the caliceal necks, there are large ve-nous anastomoses formed mainly by the veins draining the posterior half of the kidney crossing the minor calices and joining the main anterior trunks. Horizontal arches cross the calices to link the anterior and posterior vains, but also the longitudinal systems at different levels. All these arcades join each other on each plane to form large trunks flowing to the hile where they will unite and form a renal vein emptying in the inferior vena cava. The number of trunks is varies between 2 to 5, half the kidneys having three. In 70% of the kidneys, a posterior vein is observed coursing on the back of the collecting system. It will empty either directly in the cava or in the main trunk.

No other vein joins the right renal vein, whereas the left drains an important area around the vein and further along the inferior diaphragmatic vein, the left gonadal vein and the second lumbar vein.

Around the kidneys, there is a rich tenous network draining the capsule and anastomoses with the infrarenal venous system and the capsular veins.

Renal venography either in vivo or in autopsy subjects as performed by Ahlberg et al., confirmed the presence of several communications between the renal vein and others, especially colonic veins. This was best observed in cases of renal cancer with thrombotic occlusion of the renal vein. This will be outlined further when specific metastatic sites will be discussed.

Figure 11.3 shows the different pathways of spread from a renal cell cancer.

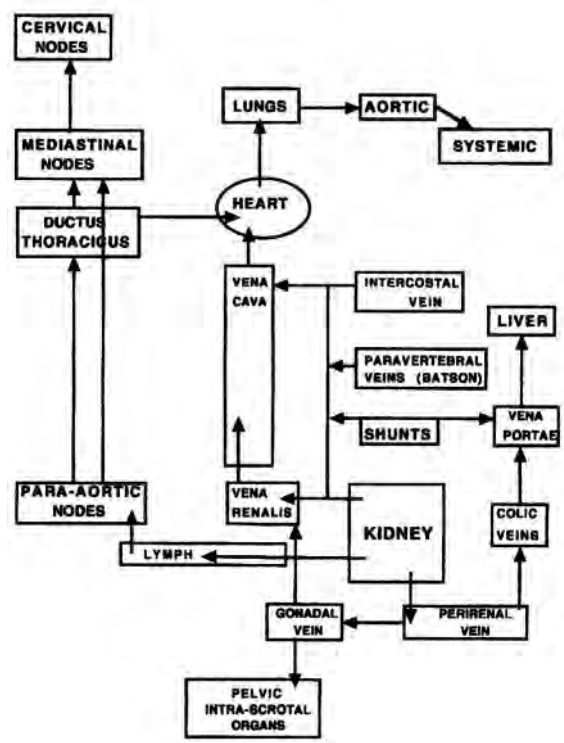

Fig. 11.3 - Diagram illustrating the spread of cells from a renal cell cancer along the different pathways.

Abdominopelvic Metastases

These may be divided into various groups; the pelvic with the urogenital organs, the abdominal (liver and

gastro-intestinal tract) and the retroperitoneal organs.

Pelvic Metastases (Urogenital)

In view of the venous connection between the renal vein at the left and the caval vein at the right, venous reflux towards pelvic organs can result in a particular pattern of metastases from renal cancers. The left kidney should result ina larger number of 'reflux' metastases as it has a direct connection with the vena spermatica/ ovarica.
As the renal vein is frequently obstructed by tumor thrombi, reflux of the venous circulation with tumor cells will reach the pelvic and even the intrascrotal content. Remember that varicocoele is a frequent first sign of left-sided kidney tumors.

Metastases to the Urinary Bladder

This is an uncommon metastatic site for renal cell cancer. While mucosal tumors have been incriminated as cellular implants from urinary flow, bladder wall metastases are rare. Venous reflux pathways along the gonadal vein is very probable, but does not adequately explain the metastases from the right kidney, unless one takes in account the collaterals between both veins.
In 90 autopsied cases of renal cell cancer, Murphy et al. found only one case metastatic to the bladder. A review by Remis et al. (1986) disclosed 18 well-documented cases. Cases reported later are on table 11.7.

Table11.7 - Renal Cell Carcinoma Metastases to the Urinary Bladder Literature Reports

Author	Pat.	Kidn	Site of M	Interval
Swanson 1982	M56	Ri	Post.wall	15 mo
Remis 1986	M68	Le	left wall	6 years
Turini 1988	M76	Ri	Anterior	simult
Acino 1988	M78	Le	Right wall	Reveal
Gelister 1992	M64	Le	not specif	3 mo
Bolkier 1993	F54	Ri	not specif.	6 mo
Chinegwu 97	M51	Le	Left wall	6 mo
Sim 1999	M69	Ri	neck	5 mo
	M55	Le	neck	60 mo
	M68	Ri	wall nos	131 mo
	M56	Ri	wall nos	2 mo
	M55	Ri	dome	16 mo
	M35	Le	neck	15 mo
	F52	Ri	no data	60 mo
Bates 1999	F47	Ri	inf.part	2 mo (')
	M66	Ri	no data	8 mo
	M64	Le	no data	6 mo
Gallmetzer 2000	M68	Ri	left wall	simult.

(') autopsy diagnosis

There are more right-sided kidneys (11:6) implicated than left-sided as far as bladder metastases are concerned.
Most of the patients have other metastases, but the symptomatology of a bladder tumor, dysuria and hematuria, calls more to attention than a 'silent' or other pulmonary metastases.
In only one case was the bladder metastasis, observed after hematuria, the first sign of a silent left renal tumor (Acino et al.).
A correlation between the side of the renal tumor and the site of the metastases at the bladder cannot be established, as the reported data are not adequate. This does not apply to vaginal metastases which will be discussed later.

Metastases to the Scrotum and Testis

According to a literature review in 1988 (Dieckman et al.), 31 cases of intrascrotal metastases from renal cell carcinoma have been reported. In 12, the epididymis was concerned, in 19, the testis and in 5, the spermatic cord. In 6 cases, the diagnosis of primary and metastasis was simultaneous. In 15 cases, the side of the primary and the involvement was the same, but in those where the side was reported, the left kidney was involved twice as freequently as the right; 14 to 7, and the left scrotum in 15 compared to 7.
Recently, a simultaneous presentation of a right renal cancer with a left testicular metastasis in a man aged 66 was reported (Steiner et al.). The crossed occurrence must be explained by the central anastomoses present between the superior part of both spermatic veins.
Recently, Lauro et al. reported on a case (M56) where the right testicular metastasis was the revealing sign of a left (contralateral) kidney cancer.
Metastasis in the spermatic cord and inguinal region were the first sign of a left renal cell cancer in two patients reported (Markovic et al.; Fallick et al.).

Metastases to the Prostate

This is very rare. We found three references, in one of which the acute urinary retention was the revealing symptomatology of a prostate metastasis masquerading as a prostate hypertrophy. A large pelvic mass was incidentally found, displacing the prostate and the bladder simultaneously with the malignant renal tumor (Yavascaoglu et al.).
At autopsy of a M64 with widespread metastasis, the prostatic bed was found to be infiltrated with metastatic renal cancer (Gelister et al.). Gross hematuria 5 months after right nephrectomy was the revealing symptom of metastasis to the prostate in another case (Moudouni et al.).

Metastases to the Penis

Twelve reports have appeared in the literature. Several presented with priapism due to venous obstruction of the pelvic vein. At least two were a first presentation (Ordonez et al.; McIntyre et al.).
Three years after a right-sided nephrectomy, a patient (M60) presented with metastases to the epididymis and spermatic cord, and another 3 years later also to the penis (Adjiman et al.).

Recently, a case metastatic to the membranous urethra was reported by Fukata et al. Goldberg et al. also have reported a case presenting in the urethra 4 years after nephrectomy.

Metastases to the Female Genitalia

Of all parts of the genital system, the vagina is the most frequently involved structure. We found 39 references, against only 10 for the ovaries, 3 for the cervix and 1 metastasis to the endometrium. In two cases at least, the ovarian 'tumor' was the revealing sign of a metastatic process.
There is also no clear correlation between the side of the primary and of the ovarian tumor (table 11.8).

Table 11.8 - Renal Cell Carcinoma
Metastases to the Ovary
Literature reports

Author	Pat	Kidney	Ovary	Interval
Stefani 1981	F68	Ri.	Le.ovary	3 mo
Buller 1983	F52	Le	Le.Ovary	First tu
Young 1992	F48	Ri	Le.ovary	First tu
	F62	Le	Ri.ovary	1 yr
	F48	Le	Le.ovary	simult
Spencer 1993	F40	Le	not stated	First tu
Adachi 1994	F46	Le	Bilateral	3 yrs
Fields 1996	F54	Ri	Le.ovary	3 yrs
Vara 1998	F66	Ri	Bilateral	11 yrs

The overwhelming majority of the vaginal metastases, about 70%, originated from the left kidney. Several are first presentation, making clinical awareness very important, primary tumors of the vagina being mostly epidermoid cancers. Of the 21 cases in table 11.9, 15 originated from the left kidney. The left wall of the vagina is the most frequently involved site, but several 'crossed' metastases are observed.

Metastases to the Abdominal Organs

Located within the retroperitoneal space, it is obvious that intra-abdominal metastases should occurr either by contiguous breakthrough from the primary, lymphatic invasion or along the hematogenous route.
Peritoneal spread is, however, hardly addressed in the literature. At autopsy, Saitoh found involvement in 10% of the patients.
If one author could report on 3 patients with retroperitoneal nodes, diffuse peritoneal invasion inclusive omental cake, it seems that this situation is probably not uncommon (Tartar et al.).
A case of left renal adenocarcinoma with two metastatic lesions in the retroperitoneal fat and in the mesenterium was reported by Nakamura et al., illustrating the double possibility of spread.

Metastases to the Liver

The liver is currently involved by metastases from the renal cancer. As usual with organs commonly involved, data are scarce in the literature as far as number, size or site and other pathology features are concerned. Data from patients subjected to excision are skewed towards operability, to the extent that they are reported.

Table 11.9 - Renal Cell Carcinoma
Vaginal Metastases as first presentation
Literature Reports

Author	Pat.	Vaginal	Kidney
Mulcahy 1970	F56	post.fornix	Left
Brun 1975	F68	left wall	Left
Carl 1977	F70	no data	Right
	F47	no data	Right
	F60	no data	Left
	F48	no data	Left
Höffken 1979	F66	ant.right	Left
	F69	left wall	Left
	F56	right wall	not given
Levin 1979	F60	right wall	Right
Sogani 1979	F47	no data	Left
	F47	anterior	Left
	F75	right ant.	Right
	F62	anterior	Left
Deprez 1981	F60	right wall	Left
Itskovitz 1981	F47	ri.dist wall	Right
O'Reilly 1984	F48	anterior	Right
Ovesen 1990	F51	left wall	Left
Rosenfeld '90	F51	left wall	Left
Torné 1994	F44	left wall	Left
Bouyounes '98	F47	--	Left
Queiroz 1999	F45	left wall	Left

Table 11.10 - Renal Carcinoma
Influence of liver metastases on other metastases
(N=687) Autopsy data of Saitoh

Site	Liver Yes N=635	Liver No N=936
Pelvi-Abdominal		
Adrenal ipsilateral	23.5%	16.1%(')
Adrenal contraleral	13.7	10.0
Kidney contraleral	28.3	23.1
Pancreas	18.4	12.7 (')
Spleen	9.3	2.6 (')
Peritoneum	19.5	12.1 (')
Intestine	13.5	9.1 (')
SupraDiaphragmatic		
Brain	8.2	13.4 (')
Lung	79.2	73.2 (')
Heart	15.0	15.1
Thyroid	4.9	5.2
Systemic		
Lymph node (any)	73.9	56.8 (')
Skeleton	20.3	20.4
Emboli	10.4	7.6

(') significant difference

Metastases can reach the liver from the lungs or directly via the portal system. Various hepatic disease can modify the portal pressure so that changes in the direction of portal blood flow can occur. Preexisting portacaval shunts are porta-pulmonary, porta-renal, splenorenal, porta-adrenal and even porta-ovarian.

These shunts may be as significant as the Batson venous plexus, a valveless plexus within which the direction of flow can change, and will explain certain 'bizarre' associations of metastatic sites.
According to Saitoh, liver-only metastases were present in about 5% of the autopsied patients. However, the liver was involved in 40% of the patients with multi-organ metastases.
There is one extensive study on the association of liver metastases with metastases in the other organs (Saitoh). A significant difference in the other associated metastatic sites was found for several organs, even for different lymph node groups (table 11.10).

Patients with liver metastases will have significantly more lung metastases, due to flow reversal in the different shunts. Saitoh found also that there were proportionnally more liver metastases in female patients and in the younger age groups.
Some hepatic metastases from renal carcinomas with hemorrhagic rupture in the peritoneal cavity causing hemoperitoneum have been reported (Wood et al.).

Metastases to the Biliary System

Metastases in the gallbladder are rare. However, renal cell cancer has been the primary in several reports of metastases in the gallbladder and bile duct.
The pathological appearance is always polypoid. All metastases are within the wall of the gallbladder or bile duct and grow intraluminally. When the bile duct is involved, symptoms of obstructive jaundice can occur. There is apparently no predilection from either kidney (table 11.11).

Table 11.11 - Renal Cell Carcinoma
Metastases in the Biliary System - Reported cases

Author	Patient	Kidn.	Pathology	Interval
Gallbladder				
Botting 1963	(not available)			
Golby 1991	M84	Le	two polyp.mass	13 yrs
Satoh 1991	M71	Ri	Polypoid	6 mo
Fullarton 1991	F43	Ri	Fundus	27 yrs
Nagler 1994	M77	Ri	Wall	2 mo
King 1995	M64	Le	intramur. Polyp.	Simul
Coskun 1995	M52	Ri	Polypoid, wall	Reveal
Pagano 1995	M62	Ri	Parietal mass	Simult.
Sparwasser '97	M46	Le	Muscular wall	44 mo
Furukawa '97	M41	Le	polypoid, wall	3 mo
Menauer 1998	F55	Ri	polympoid mass	10 yrs
Brasseur 1999	M69	Le	polypoid wall	6 mo
Bile Duct				
Kauffmann '92	M70	Ri	Choledocus	Simult
Letessier 1994	F55	??	Choledocus	17 yrs
Miyagish '96	F57	Le	Choledocus	Reveal
Stein 1999	M56	??	Choledocus	18yrs

Metastases to the Gastro-Intestinal Tract

Stomachal metastases from renal cancer are very rare. According to Odori, there should be two kinds, one that grows rapidly, and one slowly. They can present either as intramural processes progressively ulcerating or as large (voluminous) intraluminal polypoid or lobulated masses. Cases of tumors invading the posterior wall of the stomach from retroperitoneal nodes, have been reported (Laval-Jantet et al.).
Recently Hofmann et al. reported on a man aged 56, where a gastrointestinal bleeding of unknown origin was the revealing symptom of a submucosal perforating metastasis from a left sided renal cell cancer. His literature review, mostly from Japanese and Spanish, on stomachal metastases is in table 11.12.

Table 11.12 - Renal Cell Carcinoma
Metastases to the Stomach
Literature Review by Hofmann et al. (2000)

Author	Patient		Interval
Sullivan1980	M69		7 months
Nakamura 1984	M65		9 mo
Ibanez 1989	F??		2 mo
Mzarquez 1992	no data		
Kadakia 1992	M??		2 mo
Otowa 1992	F61		Revealing
Herrera 1993	no data		Revealing
Majeur 1993	M56		2 mo
Boruchowicz 1995	M48		1 mo
Blake 1995	M63		6 mo
Odori 1998	M59		4 mo
Hofmann 2000	M56	Antrum	Revealing
Picchio 2000	F58	lesser Curv	14 yrs

According to the number of reports, duodenal metastases are much more frequent. It is difficult to ascertain wether the metastases are intramural, true hematogenous, or from an invading retroperitoneal node. Here also intramural evt. ulcerating tumors or polypoid lesions are described (chapter 3).

Duodenal involvement can be either intramural or by a contiguous mass, either intrapancreatic or from a retroperitoneal node, which can occur with a tumor from either kidney.
Gastrointestinal bleeding (hematemesis or melena) is the first sign in all cases. According to a short review by Goëau et al., they are always located in the second part of the duodenum.

The topographic relation between both kidneys and the duodenum and pancreasis such that the growth of a renal cancer can be readily inferred (fig. 11.4). At the left, an enlarging kidney will push forward the splenic angle, while the stomach and the tail of the pancreas will be displaced. An enlarging right kidney will first displace the liver hilus, with the portal vein and the choledocus. The duodenopancreatic complex can also be displaced anteriorly and medially, and the hepatic angle of the colon may also be displaced anteriorly and downwards (Wemeau et al.). This shows that duo-denal involvement by renal cancer can present with several different modalities.

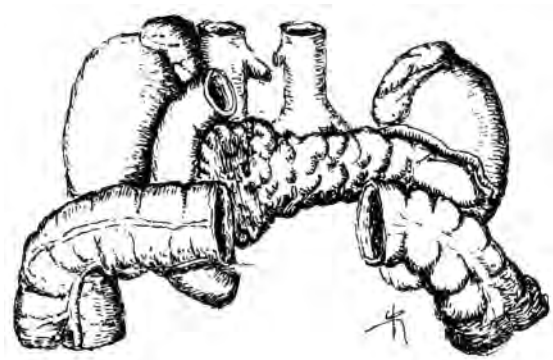

Fig. 11.4 - The anatomical relationship between the kidneys and neighbouring organs, as the duodenum, the pancreas and the colon, all located retro-peritoneally.

A rare case of intraluminal duodenal metastases was reported by Toh et al. in a woman (F59) 10 years after left nephrectomy. The metastasis was a pedunculated mass attached by a wide stalk to the posterior wall. Histology revealed that the mass originated from the serosa.
A particular type of duodenal metastases, are those described as Vaterian metastases. Gastrointestinal bleeding is the common but aspecific sign (table 11.13).

Table 11.13 - Renal Cell Carcinoma Metastases at the Ampulla of Vater Literature Reports

Author	Pat	Kidney	Interval
MacKenna 1989	M52	Left	10 years
Robertson 1990	M70	Left	12 years
Bolkier 1991	F55	Left	1 year
Venu 1991	M64	Left	11 years
Leslie 1996	F78	Left	10 years
	M53	Right	8 years

Two things are immediately evident: firstly most are from the left kidney and secondly the very long interval between diagnosis of the primary and of the metastasis.

There are several reports on metastases to the small intestine. A literature review in 1984 retrieved 13 case-reports (Py et al.). Five of them were first presentation. At surgery, several types can be encountered: a stenosing form, a nodular intramural, an ulcerated form, a polypoid and a tumoral infiltration at the mesenteric side of the gut.
A common aspect is the location at the mesenteric side of the intestine, with an intraluminal outgrowth. This can result in a voluminous tumor leading to intussusception as in the case reported by Haynes et al. It happened in a M58 about 4yrs after right nephrectomy who presented with bloody stools. A lobulated polypoid tumor from the terminal ileum protruded in the ascending colon (Deguchi et al.).

Here too, gastrointestinal bleeding, or signs of intestinal obstruction from intraluminal or mural metastases are the symptoms leading to the diagnosis.
Schröder reported on a patient with a history of 2 year of GIT-bleeding after diagnosis of the primary. The diagnosis was obtained at angiography and palliative surgery.
After having undergone a resection for a pancreatic metastasis, a patient (M63) presented 3 years later with para-umbilical pain. A solitary polypoid mass was resected from the jejunum, 10 years after radical left nephrectomy (Hession et al.).

A rare situation is the acute tumor emboli with infarction of the mesentery. A fatally evolving case was diagnosed at emergency but unsuccessful surgery (Low et al.).
A woman F75 presented with long-standing melena and diarrhea and deteriorating condition. At autopsy, the whole intestinal tract from duodenum to rectum had multiple plaque-like thickening and polypoid lesions, some ulcerated. They were most numerous in the terminal ileum. Several involved para-aortic and mesenterial lymph nodes were observed but no other metastases from the tumor of the left kidney (Shousha et al.).
Colonic metastases from renal cancers are also uncommon. Reviewing the few reported cases, one is confronted again with the high number of left kidney tumors and the very long interval between diagnosis of the primary and the metastases (table 11.14). Though many again had other metastases, the colonic symptoms were preponderant. Another remarkable fact is the high number of left colon and even sigmoid metastases. We dare to postulate that this must be explained by the collaterals existing between the lateral ramus of the spermatic (ovarian vein) and passing laterally to the kidney, anastomozing with the colonic veins (see fig.4.1).

Table 11.14 - Renal cell Carcinoma Metastases in the Colon Literature Reports

Author	Pat	Kidney	Colon	Interval
Heyman 1978	M40	left	sigmoid	20 yrs
	F56	right	cecum(')	6mo
Shousha 1986	F75	left	whole	autopsy
Ruiz 1991	M73	left	transv.-Cec	8 yrs
Thomason '91	M71	left	left	17 yrs
Zerbib 1992	M64	left	left	revealing
Tarrerias 1997	M62	left	sigmoid	5 yrs
	M72	left	right col.	4 yrs
Diaz 2000	M73	left	sigmoid	8 yrs

(') with massive retroperitoneal mass

At colonoscopy, the metastases usually appear as prominent polypoid masses, sometimes ulcerated or as obstructive lesions. At CT or surgery, rather voluminous masses are seen to be invading the colonic wall.

Metastases to the Retroperitoneal Space

As well as the retroperitoneal nodes discussed previously, these include the rare but well documented pancreatic metastases, metastases in the contralateral kidney and metastases in both adrenals. Invasion of these organs will probably occur contiguously. The previously discussed colonic metastases are also mainly located retroperitoneally.

Metastases to the Adrenal

Ipsilateral adrenal metastases can be evaluated as in most nephrectomies, the adrenal is included in the resected volume. Accurate data are laregely missing in the reports, so thatis difficult to compare left to right.
The volume reached by adrenal metastases can be very large. Contiguous invasion should be distinguished from a true metastasis. A blood supply solely from the adrenal vessels indicates true metastases. The presence of both adrenal and renal vessels suggests direct extension of the tumor into the adrenal (Campbell et al.).
At autopsy, Saitoh found ipsilateral involvement in 20% and heterolateral in 11%, but when the metastases were solitary the figure decreases to 3 and 0.7% respectively.
The best clinical data were provided by Sagalowsky et al. In 695 patients, only 30 (4.3%) patients were found to have adrenal metastases.
At the right kidney 8 of the 364 adrenals had metastases or 2.2% and at the left they amounted to 18/320 or 5.6%, or 2.5 times more. This is not stressed in their report. All further data do not take account of the right-left distribution, although they found most involvement in tumors located in the upper pole or when the entire kidney is involved. The incidence increases with stage.
Of 100 evaluable adrenal glands, only two were found to be metastatic in the series reported by Kletscher et al.

In 592 patients, only 16 (2.7%) had adrenal metastases, 10 at the right side and 6 at the left. The number of right or left nephrectomies was not stated, but no difference was noted according to the intrarenal location of the primary tumors (Seseke et al.). Only 3 of the 57 patients undergoing nephrectomy and adrenalectomy were found to have metastases in the adrenal. All were left-sided and the tumor was located at the upper pole and the adrenals were found to have invaded by continuity.
In an autopsy series, Wunderlich et al. found 272 subjects with renal cell carcinoma. In 24 or 8.82% adrenal metastases were found. Further data are in table 11.15.
Pre-operative abdominal CT was obtained in 157 patients with renal cancer. In 38 ipsilateral adrenals, an abnormality was found. Histopathology could confirm metastases in only 10 patients. The renal tumor was located in the upper pole in 6 (Gill et al.). Reviewing the literature, they found an incidence of ipsilateral involvement in 4.6%, with only half of the tumors in the upper pole.

Table 11.15 - Renal Cell Carcinoma
Adrenal Involvement
Autopsy Data by Wunderlich

Clinically Unrecognized N= 128	
1 with adrenal metastases:	
Clinically Recognized N= 144	
23 with adrenal metastases	
Ipsilateral	9
Contralateral	8
Bilateral	7
Direct extension from upper pole in 5	
Left-sided 13	Right-sided 11
The total number of right or left kidney is not given.	
Upper Pole tumors	93 : with A.M.: 8
Lower Pole tumors	83: with A.M.: 6

Two cases with almost simultaneous contralateral adrenal metastases have been reported by Foucar et al. Metachronous contralateral adrenal metastases have also been reported. In his autopsy series, Saitoh detected them in 11%. They are nevertheless rare during life. Hasegawa et al. have reported two cases occurring 6 months and a year after first surgery and Mignon et al. one year after right-sided nephrectomy.
Three other cases of simultaneous bilateral adrenal metastases have been reported by Selli et al., two from a left kidney tumor.

Several factors seem to correlate with the incidence of adrenal metastases. They are more frequent in cases of pleomorphic histology, when the renal vein is involved, when other distal metastases are present, and slightly more with a higher tumor grade. The small number of adrenal metastases in their series makes definite conclusion fallacious however.
Some data were also provided by von Knobloch et al., but the absence of data on the number of right- or left-sided tumors make conclusions difficult. They found ipsilateral adrenal metastases in 3.2% of the nephrectomized patients.
Bilateral adrenal metastases are much less common in cases of renal cancers than in breast cancers, bronchogenic cancers or melanoma. One case (M59) has been reported where both were detected at CT before surgery (Tasca et al.). A similar case with an interval of 'only' 6 years had been reported by Fox et al.
A peculiar case was reported by Duggan et al. They reported on a patient presenting with a solitary bilateral adrenal metastasis 19 years after nephrectomy. The diagnosis was first established by FNAC and confirmed at surgery.
An interesting study was reported by Soulie et al. They were able to distinguish invasion by continuity from the upper pole tumors from micrometastatic

lesions.
True Addison disease due to adrenal metastases is rare (see Chapter 3). Thirty months after nephrectomy+ adrenalectomy, a M53 presented with typical adrenocortical insufficiency due to a large heterolateral adrenal metastasis.

Our tentative conclusion is that cancers of the left kidney have a somewhat higher propensity to generate adrenal metastases. Except in the case of the invasion by contiguity, we think that venous reflux can be made responsible for ipsilateral metastases. The differ-ent small adrenal veins at the left join the renal vein close to the hile of the kidney, whereas the vein from the right adrenal drains directly to the inferior caval vein. The presence of some venal thrombosis or strain can result in some reflux towards the adrenal (fig. 11.5).

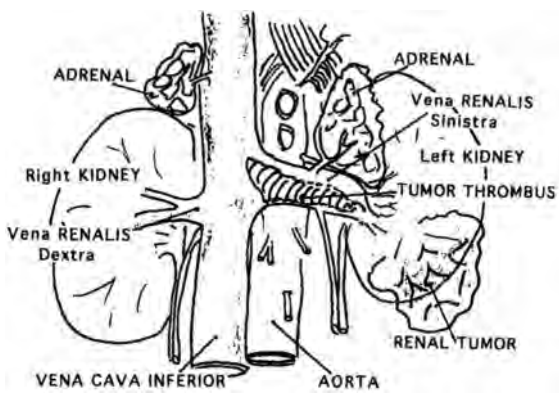

Fig. 11.5 - The venous interrelationship between adrenal and kidney at both sides, explaining the different incidence of adrenal metastases according to the side of the renal primary.

Contralateral and even solitary adrenal metastases have been reported in several patients.

Metastases to the Contralateral Kidney

Saitoh reported metastases in the Contralateral kidney in less than 1% when solitary, but in 25% when multi-organ involvement was noted. Their presence at diagnosis will create a management dilemma, as well as for the subsequent solitary metastases.
Features suggestive for metastasis are the lack of tumor capsule, multiplicity of tumors, histological similarity and a short time-interval between presentation (Fullarton et al.).
A patient (M62) with a simultaneous metastasis in the contralateral renal pelvis was described by Bergersen et al.

Metastases to the Ureter

Metastases in the ureter, either ipsi- or Contralateral are hardly mentioned in the literature. It is obvious that ipsilateral involvement could be a recurrence from the section plane, but it seems that most are either indeed hematogenous, arterial or through retroperitoneal venous plexus, or from lymphatic invasion.
A review in 1996 disclosed some 50 reported cases of ureteric involvement from renal cell (Chinegwundoh et al.), but Lee et al. could find only 8 cases reported, without giving further details. Both reports concerned contralateral involvement occurring years after surgery. Reporting on two other cases of contralateral involvement, Esrig et al. stated that of 47 reported cases, only 8 were into the contralateral ureter, including their own two cases.

Metastases to the Pancreas

Such metastases are rare, but have been discussed fairly well in the literature, as several were found solitary and could be amened to surgical resection.
Hermanutz et al. presented a case (M60) where the pancreatic metastasis perforated in the duodenum.
Pancreatic metastases should be present in patients with multi-organ involvement (Strijk et al.). Up to 1996, there are 49 cases reported who were subjected to definite resection (Hirota et al.). Remarkable is the occurrence of 20 female patients vs. 29 males, an unusual distribution in view of the low incidence of female patients with renal cell cancer. Their listed data show some insight in their occurrence (table 11.16).

Table 11.16 - Renal Cell Carcinoma
Location of metastases in Pancreas
Data from literature review by Hirota et al.

Site of Metastases	Left K.	Right K.	Bilat.
Head	9	6	1
Body	3	5	-
Tail	1	6	1
Total	1	4	-
Head & tail	2	0	1
Body & tail	3	2	2
Head & body	0	2	0
Total	19	25	5

Table 11.17 - Renal Cell Carcinoma
Pancreatic Metastases - Size and site
From data in review by Hirota et al.

	Dimensions of primary			
Site	0-2.5cm	2.6-5cm	>5cm	Multiple
Head	6	3	6	0
Body	4	4	0	0
Tail	0	3	2	2

Table 11.18 - Renal Cell Carcinoma
Pancreatic Metastases - Interval for diagnosis
From data in review by Hirota et al.

Site	Simult.	0-6mo	7-12mo	13-24mo	>25
Head	4	4	1	6	1
Body	2	1	4	1	0
Tail	1	1	3	2	1
Total	2	1	1	1	0

For cases where contiguous invasion is suspected, one would expect more left cancers invading the tail, but

the data do not support this. There are even more tail metastases for right kidney cancers. As far as the size is concerned, most are smaller than 5cm, but 15 or nearly 40% are multiple cases (table 11.17).
Smaller metastases were most frequent at the head. They are probably detected earlier as symptoms are earlier than for those at the tail. Nevertheless, several were larger than 5cm.
The interval between diagnosis of the primary and pancreatic metastases is very variable. In 9 of the 37 or 25% the diagnosis was simultaneous, but in 12 (33%) the interval was longer than one year (table 11.18). We like to mention the case presented by Jenssen, where a solitary metastasis to the head of the pancreas was found 13 years after the left nephrectomy.

Reviewing 23 patients with pancreatic metastases from renal cell cancer, Ghavamian et al. commented that it was the first metastases in 12 (52%). In 18 or 78% the metastasis was discovered more than 5 years after first surgery and in 9 or 39% after 10 years. The lesion was single in 12, 16 had the lesion at the tail, while 7 had them either at the body or the head.
Of 269 patients submitted to pancreatic resection for malignancy, six concerned metastasis from renal cell cancer. Four were female patients. The mean tumor size was 4cm(range 1.5 to 8cm) and the metastases were multiple, up to 5 in 3 patients (Faure et al.).
A metastasis in the head of the pancreas mimicking a primary pancreatic cancer occurred in a woman (F61) 18 years after left nephrectomy (Sahin et al.). Portal et al. have reported on a patient (M69) who developed a solitary metastasis in the head of the pancreas 7yrs after first surgeryand 4 yrs later in the tail.

Modern imaging methods allow a more accurate diagnosis than decades ago, but the imaging features are not always specific. Screening US-graphy is useful but hardly diagnostic of the precise nature of the metastases. According to Ghavamian et al., the CT characteristics resemble those of the renal primary, appearing as well-defined masses, predominantly hyperattenuating relative to normal pancreas tissue. Larger lesions have central areas of necrosis. The density difference at CT with normal tissue is sometimes minimal. Contrast enhancement can be indicative as several are hypervascular, but differential diagnosis with islet cell tumors is necessary (see Chapter 2).
Pancreatic metastases occurring 20 years (Audisio et al.) or 25 years after first surgery (Temellini et al.) have been reported.

Supra-Diaphragmatic Metastases

Metastases to the Central Nervous System

Brain metastases are found at autopsy in about 10 to 15% of patients. They are more frequent when the patient has lung metastases, making the arterial hematogenous route most probable.
A retrospective study by Marshall et al. revealed brain metastases in 14 of 106 patients with renal cell cancer. In 3 patients, or 21%, the lesion was asymptomatic.
Kidney cancers are most often associated with single metastatic foci. They share this propensity with cancers of the colon and other abdominal and pelvic tumors.
A number have been reported as first sign, either with epileptic symptoms, hemorrhagic syndromes or other.
A few neurosurgical series have been reported, but only one study was found reporting pathology data (table 11.19). In 66 patients, 104 metastases was identified, and in half of them the metastasis were solitary. Remark that 70% of the supratentorial metastases were located at the left side of the brain and of the 71 multiple metastases, 54 or 76% also were at the left side. As no other publication has reported comparable data, we cannot conclude to a preferential site.

Table 11.19 - Renal cell Carcinoma
Brain Metastases - Data of Culine et al.

	Involved Hemisphere		
Site	Left	Right	Total
Frontal	13	11	24
Parietal	25	9	34
Temporal	12	3	15
Occipital	14	4	18
Infratentorial	--	--	13
Total	64	27	104

Brain metastases were found in 5% of the patients at diagnosis. They are rarely the first manifestation as in the case of Fitzgerald et al. A man (M63) presented with recent focal seizures and several brain metastases were seen at CT, metastatic from an asymptomatic right kidney cancer.
The median interval to occurrence is 7years (Ammirati et al.). In the few reported series the median interval was 1 year. Late solitary metastases in the brain are rare. Ammirati et al. reported on one late, 13 years, cerebellar metastasis in a woman F63. Two late solitary cerebral metastases, one after 13 and one after 17 years, were reported by Cervoni et al.
Symptomatology correlates with the anatomic location and may include motor deficits and disorientation, but morning headache is a frequent feature.

Rare cases of metastases at the sinus cavernosus have been reported (Spell et al.) and one at the cerebellopontine angle, presenting as a tumor bleeding from the ear, due to a large lesion occupying the site and eroding the petrous and mastoid bone (Bhatoe et al.).
Only one report concerned specifically a leptomeningeal carcinomatosis (Crino et al.).
A solitary choroid plexus metastasis was reported in a young woman (F47), diagnosed simultaneously with a left renal mass, confirmed as adenocarcinoma (Raila et al.). A literature review by the authors retrieved 5 other cases from renal cell carcinoma, of the 15 reported, mainly in the Japanese literature.
A CP-angle syndrome was the metastatic revealing

sign of a renal cell cancer in a M44 (Caldas et al.).
One case of hematomyelia due to seeding into the rachidial canal after resection of a cerebellar metastasis was reported (Kawakami et al.). The rare site of cauda equina, intradural and extramedullary, was reported as solitary in a M84, several years after a left nephrectomy (Maxwell et al.).
The rare intramedullary spinal cpord metastasis was observed at the level of C2-C4 associated with a syrinx in a M63, 11 years after the diagnosis of a right renal cell cancer (Ateaque et al.).

As for many metastases in the renal cancer, they can appear many years, even decades after the diagnosis of the primary tumor.

Metastases to the Pituitary

While relatively common in breast and bronchial cancers, metastases in the pituitary from kidney cancer is rare. We found six cases reported in the literature (table 11.19). In 1965 Kradijan et al. reported a patient with this metastasis 31 years after nephrectomy (report not available). A few other cases have been reported but the reports could not be obtained.

Table 11.19 - Renal Cell Carcinoma Metastases in the Pituitary Gland Case reports in literature

Author	Pat	Kidney	Symptom	Interval
Anniko 1981	M59	Ri	panhypopituitarism	9yrs
James 1984	M75	Ri	visual deficit	9yrs
Eick 1985	M66	Ri	adynamia	Reveal
Charach 1990	M77	ns	diabetesinsipidus	Reveal
Koshiyama '92	M57	Ri	finding at staging	
Weiss 1993	M59	Ri	impotence,vision	Simult

Remark that all patients were men and the primary kidney tumor was at the right in all. Three were revealing situations. The symptomatology was either diabetes insipidus, visual disturbances or patent panhypopituitarism.

Thoracic Metastases

Reviewing records and chest roentgenograms of 46 patients with renal cancer, Kutty et al. found intrathoracic metastases in 25, or 54%. Lung metastases were discerned in 14, alone in 10 and with mediastinal or pleural metastases in 4. Mediastinal lymph node were present in 13, as the sole finding in 6 of them. This more or less demonstrates the double pathway the cells from the renal tumors follow, firstly the central venous system along the caval vein and secondly the lymphatic system towards the mediastinal nodes (fig. 11.3).

Pulmonary metastases are in the present CT-era asymptomatic in about 75%. Mainly in renal cancer, the typical 'canon-ball' pattern is observed.
Parenchymal lung metastases are relatively frequent, but clinical data according to stage and follow-up are lacking. Again, in spite of the numerous surgical series discussing metastasectomy, no pathology data as statistics on size, bilaterality or location within the lungs are at hand .
We found some data in the report of Fourquier et al. The mean interval between previous nephrectomy and the diagnosis of lung metastases was 3 years (range 0-18 years). Bronchoscopy was normal in 41 of the 50 patients.There was an intra-luminal proximal tumor in 4, a distal one in 3 and in two an external compression was observed.
Pulmonary metastases (of the operated patients) were bilateral in 18, solitary in 19 and multiple unilateral in 13. They were located at the periphery in 37 and centrally in 13.
The data on the pathology of the lung metastases, certainly at hand in several data-banks, are interesting and shoiuld be reported eventually correlating them with the side of the renal tumor.

We like to mention that in 19 patients subjected to pulmonary surgery, the malignity was confirmed in 16, while the three others had either tuberculoma, chondroid hamartoma or a focus of anthracosis (Cozzoli et al.). This raises the problem of the pathology of a coin lesion.

Another form of metastatic involvement of the lung is the endobronchial one. While this is not uncommon at autopsy, more important are the cases presenting with endobronchial metastases as first sign.
According to Akhtar et al., only 12 cases with revealing endobronchial metastases should have been reported. The symptomatology is usually dyspnea, cough, chest pain and retro-obstructive infections. Hemoptysis is common and expectoration of tumor tissue in the form of ragged bronchial casts, has been reported (Jariwalla et al.).
At bronchoscopy, the lesion usually presents as a nodular ulceration, but massive infiltration from a tumorous node has also been observed.
The diagnosis is of the utmost importance in order to avoid inadequate treatments, stressing the responsability of the pathologist.
Reporting on 4 patients with endobronchial metastases, of whom one was a type 1 presentation, Irvine et al. stressed the connection with mediastinal hilar metastatic adenopathies, probably the underlying pathology for the endobronchial invasion.

Mediastinal or hilar lymphadenopathy is a rare presentation form of renal cell cancer. Cell dissemination from the retroperitoneal nodes goes to the thoracic duct, but reflux of tumor emboli into the bronchomediastinal trunks, paratracheal lymphatics, bronchopulmonary and interlobular lymphatics may result in incompetence of the lymphatic valves. This no doubt explains hilar adenopathy in renal cell carcinoma. Such reflux has been observed in lymphography in about 5 to 10% of the patients. This also explains the

low incidence of hilar nodes (Reinke et al.). The report of Kutty et al. with an incidence in 25% of their renal cancer patients suggests that it is probably underreported.
Recently Fritscher-Ravens et al. reported on 7 patients with positive mediastinal nodes at FNAC obtained at endoscopic US-graphy from a group of 111 patients (malignancy not specified). In 4 of the patients, the mediastinal nodes were the first sign of renal (clear cell) cancer.
A 53-year old man presented with a right sided pleural effusion, pleural and pulmonal metastases and a left sided renal cell carcinoma without any other metastases (Fischer et al.).
Recently one patient (M74) has been reported in whom, on the basis of the CT-findings, the diagnosis of pleural mesothelioma was first posed, because of an extensive pleural involvement without any other location. At biopsy, however, it was found to concern a renal cell carcinoma effectively confirmed (Azuma et al.). The authors found 11 similar cases reported in the literature.

Cardiac Metastases

As in several other cancers, the heart can be involved either in the wall (myocard) or intracavitary by a growing tumorous thrombosis from the renal vein through the inferior caval vein. The latter is the most common feature of cardial involvement in renal cell cancer.
True metastases to the heart from renal cell cancer have rarely been reported. The most frequent are intramural metastases within the right ventricle (table 11.20), some with ventricular outflow obstruction.

Table 11.20 - Renal Cell Carcinoma
Cardiac Metastases Reported

Author	Pat.	Kidney	Site	Interval
Gordon '73	M58	??	Ri.Ventricle	Revealing
Johnson '82	M49	Le	Tamponade	Revealing
Goldman '85	M61	Ri	Ri.Atrial	Simult.
Atay 1987	M67	Ri.	Ri.Atrial	3 mos
Gindea '88	M74	Le.	Ri.Atrium	Revealing
Shih 1991	M62	??	Le.Ventricle	3 mos
Sobue 1993	F60	Ri.	Le.Ventricle	6 yrs
Reynen '95	M61	??	Ri.Ventricle	10 yrs
Minale '95	M63	??	Ri.Ventricle	19 yrs
Carroll '94	M53	Le.	Ri.Ventricle	Revealing
Riccione'96	M64	Le	Le.Ventricle	5 weeks
Santo 1998	M56	Le	Ri.Ventricle	Revealing
Islam 1998	M39	??	Tamponade	Revealing
Fogel 1990	M77	Le	Le Atrium	6 yrs
Sivaram '95	M64	Le	Le.Atrium	>2yrs
Patane '96	F58	Le	Le.Atrium	5 yrs

Remarkable is the presence in the list of three cases with metastasis in the left atrium, without any lung involvement and without the presence of a left-right shunt in the heart. The case described by Sivaram et al. involved a tumor thrombus extending from a pulmonary metastasis within the pulmonary veins, extending to the left atrium.
The three cases of left ventricular wall and three left atrial metastases without an intracardiac septum defect and normal chest-X-rays findings can only be explained by cells passing through small arteriovenous shunts in the lungs.
We are aware of two cases of tamponade with pericard effusion and revealing the renal cancer (Islam et al.). A 60 year old woman presented at Emergency with left flank pain and hematuria. A chest X-ray showed enlargement of the heart and a tap confirmed an effusion with positive cytology (Schellhammer et al.). In the case (M49) reported by Johnson et al., the renal tumor was only revealed at autopsy.

One case with a metastasis in the atrio-ventricular node must be mentioned. It was found at autopsy in a woman (F48) with skeletal metastases and long-standing bradycardia (James).

Venous Invasion / Involvement

Virtually all malignant renal neoplasms have a strong predilection to invade regional veins. This tendency is usually confined to the ipsilateral renal vein, but can extend towards the vena cava inferior even up into the right atrium. The incidence is variously quoted from 8 to 67% (Schechter et al.). Hermanek et al. quote an incidence of 77%, while Weisser cites 35% (table 11.21).

Table 11.21 - Renal Cell Carcinoma
Frequency of invasion of veins
Literature data

	Hermanek N=188 (1976)	Weisser N=5213 (1976)
No Invasion	23%	65%
Invasion (histol.)	28%	all :35%
Invasion (macro)	49%	
in branches of renal vein:		16%
in trunk of renal vein		30%
within vena cava		3%

Table 11.22 - Renal Cell Carcinoma
Tumor Features and incidence of Caval Thrombus
Data of Hermanek et al.

Feature	Thrombus Present Histologic	Ev.Macroscopic
Tumor Diameter		
up to 30 mm	36.4%	none
31-50 mm	39.1%	15.2%
51-100 mm	36.2	40.0
>100 mm	18.4	71.3
Spread		
Confined to kidney	25.9%	10.6%
Fibrous caps.+ pelvis	38.1	41.5
Perirenal	27.8	65.5
Malignancy Grade		
Grade 1	24.2%	22.6%
Grade 2	35.5	37.4
Grade 3	26.8	65.5

Reviewing the literature in 1982, Richaud et al. found an incidence of 20 to 30% of which 5 to 10 % within the vena cava. Ten to 20% of these had reached the right atrium. The origin of the thrombus was in the right kidney in a ratio of 2 to 3:1 or sometimes even more.

In a subsequent review, based on 426 patients, Hermanek et al. reported on the influence of the pathological features of the renal tumor (table 11.22). They remarked an increase with size, with increasing invasion and with grade of the primary. Intracaval extension to the right atrium is a life-threatening situation that may result in fatal tricuspid valve obstruction or pulmonary embolization.

The level to which the thrombus extends within the inferior vena cava is defined according to Neves and Zincke, and more or less mirrors the surgical difficulty to be encountered (fig. 11.6). MR imaging is appropriate for its determination, while echocardiography is certainly important for the screening of cardiac problems. The presence of a pro-gredient thrombus in the renal vein and further will initiate a process whereby venous blood will seek an alternative pathway along several shunts between the renal vein and prevertebral plexus.

This is illustrated in figure 11.7, where the blood has found its way in the azygos system.

Obstruction of the inferior vena cava is asymptomatic in 50 to 75% of patients (Shahian et al.), implicating the insidious character and danger at surgery, when this was not explored by US-graphy or CT. Most of these patients have no other metastases, making them good candidates for aggressive treatment however.

Recently, different cases have been reported in whom at arteriography connections exist between the renal and the inferior mesenteric vein (Inoue et al.). During venography for chemo-embolization, Tsushima et al. observed collaterals between the left renal vein and the mesenteric or splenic vein, resulting in a shunt between the systemic and the portal circulation. This can very well explain the occurrence of liver metastases without pulmonary involvement.

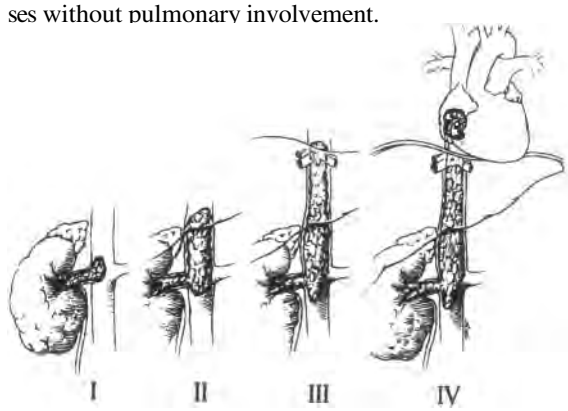

Fig. 11.6 - Classification of the extent of the tumor thrombus within the inferior vena cava (from Nesbitt et al., with permission)

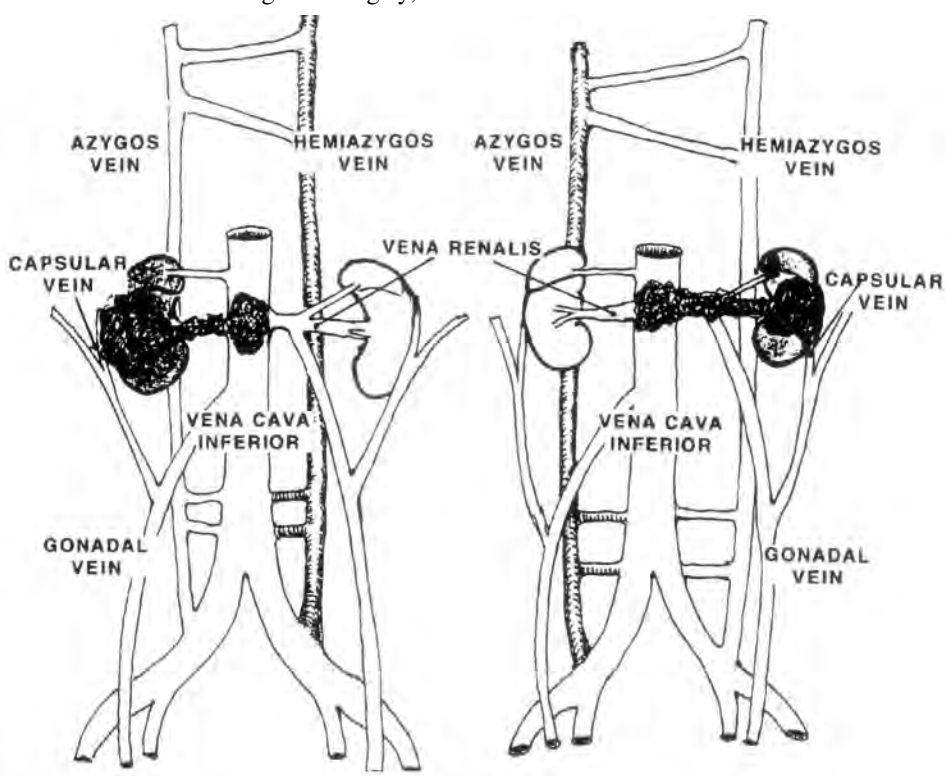

Fig.11.7 - The development of collateral circulation in cases of thrombosis of the vena renalis. The situation differs according to the involved kidney. The veins that are colored black are committed for collateral circulation

A number of cases have been reported diagnosed after sudden death or accident fatalities (Moar).

Ophthalmic Metastases

Metastases to the eye or orbit are not as common as in other primary tumors. Reviewing the files of the University Hospital of Hamburg, Damms et al. found renal cell cancer to be responsible for only 10.8% of all 36 ocular metastases encountered.
The fact that some authors could report more than one case allows to think that several are not reported. As Haimovici et al. emphasizes, the reddish or reddish-orange appearance of some choroidal metastases from renal cell carcinoma may help to distinguish them from amelanotic choroidal melanoma, but this color is present in only a few of these metastases.
The reported cases, as far as they are available, are summarized in table 11.23. There are several revealing cases (type 1) and also several occurring many years after first surgery.

Table 11.23 - Renal Cell Carcinoma
Ophthalmic Metastases - Literature Reports

Author	Pat	Kidney	Site	Interval
Choroid				
Laszczyk 1975	M56	??	Ri.	no data
Voigt 1977	M41	Li	Ri temp.	16 mo
Kinderman '81	M58	Le.	Le.	9 yrs
Pau 1981	M55	??	Le.nasal	5 yrs
Holbach 1990	M75	??	Ri.poster	16 yrs
Damms 1991	F82	??	Le.	11 yrs
Haimovici '97	M54	Ri.	Le.post	18 yrs
	M62	Le.	Le.	Revealing
	M48	??	Ri.infer.	Revealing
	F66	Le.	Le.super.	9 yrs
	M77	Le.	Ri.Inf.Temp	6 yrs
Orbit				
Howard 1978	M47	Le	Ri.orbit	Revealing
Kinderman '81	M58	Ri.	Ri.orbit	15 yrs
Denby 1985	M65	Ri.	Ri. f..lacr.	Reveal.
Parnes 1993	M53	Ri.	Ri.orbit	Revealing
Wolin 1993	M66	Le	Ri.orbit	Revealing
Schmidt 1994	M69	Ri.	Le.orbit	2 yrs
Bersani 1994	M50	Ri.	Le.orbit	15 yrs
Holt 1995	M56	Ri.	Le.orbit	Revealing
Holt 1955	M60	Le.	Le.orbit	Revealing
Iris				
Wyzinski '81	M60	Le	Both iris	Simultan
Portnoy 1991	M65	Le	Le.iris	Revealing
Ware 1999	M70	Le	Le.iris	Revealing
Eyelid				
Kinderman '81	M66	Ri	Le.upper	15 mo

Head and Neck Metastases

Renal cancers have a tendency, more than any other malignancy, to metastasize in the Head and Neck. Metastases have been reported in almost all remote corners of the region. The most 'fertile' sites for these tumor cells are the sinuses and the salivary glands and the thyroid, as will be discussed further.
Asmentioned in Chapter 6, renal cell cancer is the most common primary metastasizing to the nasal cavity and sinuses. A preferential site is probably the maxillary antrum, occurring in about 50% according to some authors.
This unique affinity to the sino-nasal site is somewhat difficult to explain, but must involve an interplay between cytological, biochemical and vascular properties and other host elements.
An important number of the reported cases are first presentation, but this is due more to the silent local evolution quite a number of renal cancers have. The first presentation is always a 'beautiful' diagnosis, when recognized and more amenable to publication than one occurring during the follow-up, mostly together with other metastases. Nevertheless its lesson is that one has to think about renal cancer when the presentation in the head and neck occurs, and certainly when the presentation is an excessive bleeding.

Table 11.24 - Renal Cell Carcinoma
Head and Neck Metastases
Literature Reports- Bibliometric analysis

Sites in descending order of reference (')

Nasal Cavity	21	Tongue	13
Mandibula	18	Tonsil	10
Sinus any	17	Gingiva	8
Ethmoid	5	Ear	6
Frontal	3	Palate	4
Combined	9	Maxilla	2
Larynx	15	N.O.S.	10

(') some references reported on more than one patient

A good way to obtain an insight in the relative frequency of the various different H&N sites metastatic from renal cancer is counting the number of the respective references. We were able to collect 117 references, reporting one or more case/site (table 11.24).

For completeness, we should mention the case reported by Kuntzer et al. Gradual chin numbness was the revealing sign of different bone metastases, among them one in the mandible, of a right renal cell cancer.
Sinonasal metastases are the most frequent H&N site for renal cancer. Several are located in the rare site of frontal and ethmoidal sinuses, a preferred site for renal cancer compared with other primaries.

The literature on that site was reviewed in 1995 by Sesenna et al., retrieving 32 cases. There were 9 female and 17 male patients, while gender was not reported in the other. In 11 or 33%, the metastasis was the presenting symptom of an unknown renal cancer. The longest interval was 20 years after first treatment, but most frequently metastases occurred within 2 years.

The symptomatology was almost always 'profuse' epistaxis, with nasal obstruction or associated with ophthalmic symptoms, when more advanced.
Within the oral cavity, the tongue, palate and gingiva have been reported as metastatic sites (table 11.25).

Remark that of the 32 cases listed, 17 are female patients or more than the normal distribution of the primaries between both genders.
A literature review by Bom et al. (1981) found 13 other cases, dating back to 1931, of tonsillar metastases from renal cell cancer. Okabe et al. found 7 other cases of lingual metastases in their 1992 review.
While many patients had solitary metastases, about half were mentioned as having several other metastatic sites including the lung and bone.

Table 11.25 - Renal Cell Carcinoma
H&N metastases (non-sinonasal) reported

Author Year	Pat	Kidney	Site	Interval
DelCarmen 1970	M77	Le.	Tongue	3 wks
Miyamoto 1973	M60	ns	Tongue	5 mo
Okabe 1992	M58	Le	Tongue	1 yr
Airoildi 1995	M51	ns	Tongue	6 mo
Aguirre 1996	F82	Le	Tongue	Reveal
Sidhu 1982	F32	Ri	Le.mandible	Reveal
Fitzgerald 1982	M63	Ri	Ging.MaxillaRi	1 mo
Akdas 1987	M55	Ri	Maxilla	6 yrs
Zachariades'89	M78	Ri	Le.mandible	2 yrs
Jones1990	F62	Le	Ri mandible	Reveal
Jones 1990	F52	Ri	Ri mandible	Reveal
Carroll 1993	F24	Le	Ri mandible	Reveal
Carroll 1993	M18	Le	Ri mandible	Reveal
Lee 1998	M76	Le	Maxilla	Reveal
Guyot 1999	F83	Le	Ri mandible	Reveal
Miyamoto 1973	F81	ns	Le audit.can.	Reveal
Ferron 1982	F69	Ri	Le audit.can.	8 yrs
Zirul 1983	F6	Le	Ri.audit.can	2 yrs
Goldman '92	M62	ns	Ri audit.can	7 yrs
Ingelaere '97	M50	Ri	Ri.audit.can	Reveal
Lansigan 1973	F74	Ri	Uvula	Reveal
Susan 1979	M53	Le	Palate	Reveal
Susan 1979	M62	Ri	Palate	Reveal
Lutcavage '84	M55	Le	Palate	6 mo
Menauer 1998(')	F55	Ri	Palate	10 yrs
Miyamoto 1973	M79	Le	Ri.aryepiglott	17 yrs
Ferlito 1987	M73	Ri	Subglottis	Reveal
Maung 1987	M48	Le	Ri.cord	13 yrs
Greenberg 1992	M55	Le	Subglottis	Reveal
Marlowe '93	M54	Le	Ri larynx	Reveal
Hittel 1995	F42	Ri	Ant.commiss.	6 yrs
Issing 1996	F73	ns	Ri.false cord	6 yrs
Dee 2000	M48	Le	Supraglottis	1 yr
Draizin 1978	F57	Le	Ri tonsil	2 yrs
Brownson 1979	F??	Le	Le tonsil	11 yrs
Brownson 1979	M54	Le	Le tonsil	Reveal
Bom 1982	F54	Le	Le tonsil	7 yrs
Steffens 1984	F64	Le	Tonsil	6 mo
Hussain 1988	M55	Ri	Ri tonsil	5 yrs
Green 1997	M47	ns	Ri tonsil	2 yrs
Menauer 1998(')F55		Ri	Tonsil	10 yrs

(') same patient, two metastatic sites

Metastases to the Salivary Glands

We found 27 reports on the subject. About half were first presentation as a tumorous suspicious swelling in the parotid, for two cases in the submandibular gland (table 11.26). They are difficult to differentiate from the more frequent primaries, particularly when they are first sign metastasis.

Incidentally of the 9 cases, 8 were at the left parotid. In the cases with metastases during follow-up, the interval time was frequently several years.

Table 11.26 - Renal Cell Carcinoma
Revealing Metastases in the Salivary Glands
Literature reports

Author	Pat.	Site	Kidney	Histol.
Gandon 1977	M74	Le.Parotid	Right	CC(')
Sist 1982	M62	Le.Parotid	Right	CC
Bedrosian 1984	M61	Le.Submand	Left	CC
Melnick 1989	M72	Le.Parotid	Right	CC
Owens 1989	M55	Ri.Parotid	Left	CC
Pisani 1990	M59	Le.Parotid	Left	CC
Coppa 1990	M42	Le.Parotid	Right	CC
Sykes 1995	M59	Le.Parotid	Left	CC

CC: clear cell cancer

Table 11.27 - Renal Cell Carcinoma
Metastases in the Thyroid Gland - First Presentation
Literature data

Author	Patient	Kidney	Present	
Welti 1966	M58	Le	Goiter	Reveal
Gault 1973	F69	Le	Goiter	Reveal
Kniemeyer 1981	F69	Ri	multinodular	Reveal
Lehur 1983	F37	Le	Goiter	Reveal
Janser 1986	M71	Ri	Goiter	Reveal
DalFabbro 1987	F62	Ri	Nodule (Ri.)	Reveal
Halbauer 1991	M62	Le	Ri.lobe	Reveal
Murakami 1993	M63	Ri	Goiter	Simult
Hadjadj 1995	F82	Le	Whole gland	Reveal
Palazzo 1999	M63	Ri	Ri.lobe mass	Reveal

Metastases to the Thyroid gland

The thyroid is well known as a metastatic site for renal cell carcinoma. We found about 40 references since 1975.
The metastases can present as one or more nodules or as an infiltration of a whole lobe or of the whole gland. A few have clear hyperfunctioning signs. Several are first-sign metastases.

A literature review in 1989 came up with 36 cases, of which 19 (53%) were female patients. In eight patients the thyroid metastases was the first sign of an unknown renal cell cancer (Green et al.) (table 11.27).

Overall we retrieved 36 cases, of whom 8 were revealing cases. There is again a relative preponderance of 20 females vs 16 males. The left kidney was the primary in 18 and the right in 15, 1 being bilateral and in two the side was not stated (Table 11.28).
The patient reported by Avisse et al. is a peculiar one. She presented successively only with metastases within an endocrine gland, first in the pancreas and

heterolateral adrenal, and later in the thyroid.

Table 11.28 - Renal Cell Carcinoma
Metastases in the Thyroid Gland - During Follow-up
Literature data

Author	Patient	Kidney	Present	Interval
Welti 1966	F56	Le	goiter	10 yrs
Welti 1966	F61	n.s.	goiter	15 yrs
Welti 1966	M56	Le	goiter	3 yrs
Fridberg 1969	M88	Ri	Ri.lobe	16 yrs
Fridberg 1969	M46	Ri	Ri.lobe	3 mo
Fridberg 1969	M38	Le	swelling	12 yrs
Fridberg 1969	M66	Le	diffuse	9 mo
Vaglini 1975	F56	Le	multinodular	10 yrs
Madore 1975	F58	Ri	diffuse enlarg	7 yrs
Becourt 1980	M65	Le	hyperthyr.Ri	4 yrs
Becourt 1980	M81	Ri	Le nodule	8 yrs
Becourt 1980	F68	Ri	nodule	5 yrs
Treadwell 1981	F63	Le	swelling left	13 yrs
Kniemeyer '81	M66	Le	Ri nodule	5 yrs
Kniemeyer '81	F57	Ri	Multinodular	12 yrs
Goeau 1983	F71	Le	Ri.nodule	6 yrs
Shima 1985	F69	Le	Le.nodule	20 yrs
Janser 1986	F49	Le	goiter	27 yrs
Janser 1986	F73	Ri	goiter	11 yrs
Janser 1986	F66	Ri	goiter	11yrs
Janser 1986	M70	Ri	Le.nodule	2 yrs
Prati 1988	F54	Ri	Ri nodule	6 mo
Fullarton '91	F43	Ri	Ri nodule	22 yrs
Hudson 1991	F60	Bil	Le.lobe mass	13 mo
Letoquart '91	M55	Ri	Multinodular	5 yrs
Niiyama 1994	F72	Le	Le.multiple	3 mo
Hadjadj 1995	F82	ns	whole gland	24 yrs
Innocente '95	F51	Ri	Ri.nodule	12 yrs
Ozdemir 1995	M45	Le	Ri lobe	11 yrs
Avisse 1995	F39	Le	cold nodule	12 yrs
Frenot 1995	F47	Ri	Ri.lobe (')	6 mo
Siekierska '97	F49	Le	Le nodule	18 yrs
Bertin 1999	M77	Le	Ri.whole lobe	3 yrs
Palazzo 1999	M76	ns	Neck mass	3 yrs
Palazzo 1999	M79	Ri	Neck mass	9 yrs
Palazzo 1999	F58	Ri	Ri.mass	3 yrs

(') with hyperthyroidism

Table 11.29 - Renal Cell Carcinoma
Bone Metastases - (N=542 autopsies)
Data of Saitoh

	All	Solitary(N=33)
Skull	6%	9%
Spine		
Cervical	4	12
Dorsal	24	27
Lumbar	18	9
Sternum	7	21
Ribs	24	39
Clavicle	2	3
Scapula	4	--
Humerus	4	9
Pelvis	12	36
Femur	12	27
Other	7	0
Unknown	(26%)	--

Systemic Metastases

As systemic metastases we have included those in bone, skin and muscle

Bone Metastases

Autopsy data of Saitoh showed an incidence of 542/1451 or 37.5%. The distribution of the metastatic sites is somewhat different to that of other cancers, as there are proportionally more at the peripheric site (table 11.29). Autopsy data constitute a final status and their relevance depends on the diligence of the pathologist. The number of metastatic site is certainly higher than in clinical data. Such data are, however, scarce. Several surgical or orthopedic series contain a number of patients, but they concern only patients with impending or pathological fractures.

Table 11.30 - Renal Cell Carcinoma
Bone Metastases -Radiology Features in Long Bones
Data of Forbes et al. (N=47)

Location	Metaphyseal	26	55%
	Extension to Diaphysis	9	19
	Extension to Epiphysis	12	26
Modification	Well-defined margin	7	15
	Poorly defined margin	40	85
	Cortical destruction	40	85
	Intramedullary erosion	7	15
	Lytic matrix	47	100
	Soft-tissue mass	14	30
	Pathologic fracture	20	43

Of 1,668 patients with renal cancer seen at the Mayo Clinics between 1964 and 1974, 167 or 10% had some bone metastases. It was the first sign in 63 patients. The bone metastases were found at staging in 24 patients and in 80 during further evolution (Forbes et al.). Lower spine and pelvis were the most frequent involved sites. Their data on the radiographic appearance are interesting (table 11.30). Most lesions destroy the cortical bone and invade the surrounding soft tissue. In renal cell cancer, the bone metastases are invariably osteolytic, but they have an expansive trend (hypertrophic) more frequently than in other primaries. The overall radiological aspect is well delineated by the following table 11.31 based on a report of Cook et al.

Table 11.31 - Renal Cell Cancer
Radiological aspects of Bone metastases
Modified from Cook et al.

Single or Multiple
Lytic aspect, occasionally septate, 'soap bubble'
Expansile hypertrophic type common (10-20%)
Axial skeleton most frequent, but limbs not rare
Infrequent periosteal reaction
Infrequent reactive bone formation
Occasional associated soft tissue mass
Pathologic fractures common (limbs not rarely affected)

Osteoblastic metastases should be rare, but are probably underreported, at least for renal cancer.

Of 947 patients, 252 experienced some bone metastases after diagnosis and during further clinical course (Swanson et al.). Their data are particularly interesting and shown in table 11.32.

The metastastic sites of the skeleton are in table 11.33. While the spine, particularly the thoracolumbar spine has the highest frequency, the number of rib metastases is relatively high when compared with other osteophylic cancers. Remark also the relative high number of metastases in the shoulder, the humerus and femur.

Table 11.32 - Renal Cell Carcinoma
Features of Bone Metastases
From Swanson et al.

Bone is first metastasis in	131 (52%)
Solitary in	75 (29%)
Multiple at diagnosis in	56
At diagnosis bone + soft tssue	69
At diagnosis soft tissue, later bone	52
Bone as first complaint in	121 (48%)
Present with pathological fracture	37 (14%)
Fracture in clinical course	34

Table 11.33 - Renal Cell Carcinoma
Bone Metastases - Clinical Data in 252 patients
Data of Swanson et al.

Skull	16.3%	Thorax-Pelvis	
Maxilla	0.8	Ribs	38.9%
Mandible	1.2	Clavicle	6.0
Spine		Scapula	15.5
Cervical	8.7	Ilium	30.2
Dorsal	33.3	Ischion	9.9
Lumbar	31.7	Pubis	3.6
Sacrum	9.1		
Upper Limb		Lower Limb	
Humerus	20.6	Femur	27.0
Radius	2.8	Lower leg	1.2
Ulna	0.8		

Table 11.34- Renal Cell Carcinoma
Bone Metastases - Clinical Data in 38 patients
Data of Althausen et al.

First Site (38 sites)		All Sites in Evolution	
Axial		Axial (58 sites)	
Pelvis	7	Pelvis	24
Thoracic Spine	4	Ribs	11
Cervical spine	1	Spine (all)	13
Lumbar spine	1	Skull	8
		Sternum	2
Non Axial		NonAxial(66 sites)	
Scapula	5	Scapula	13
Humerus	5	Humerus	19
Femur	10	Femur	19
Tibia	2	Tibia	7
Clavicle	1	Fibula	2
Fibula	1	Foot	2
Foot	1	Patella, ulna, radius, Carpus each 1	

Data comparing locations at diagnosis and during evolution have been provided by Althausen et al. in 38 patients (table 11.34). Renal cancer was discovered in 17 patients at the same time as the metastatic lesion in the bone. In 8 of them, the bone problem was the first complaint.

In 21 patients, the bone metastases were uncovered during follow-up after the treatment of the primary. The comparative data are in table 11.34 giving the site of the first metastases and all the sites finally observed at death.

Of the first site, 65% are non-axial (appendicular) or located in the limbs, which is a quite high proportion. After further evolution this has only dropped to 53%.

The metastasis-free interval ranged up to 22.4 years, with a mean interval of 3.0 ± 5.4 years.

Overall, one metastatic site remained the only one during further evolution in 13. The time interval between the first metastasis and the 'next' ranged up to 16 years, with a mean of 2.9 ± 5.3 years.

The study by Arkless is a remarkable one. He first found that in 40 patients with bone metastases, 25 or 62.5% had axial metastases. He noted further that in 15 patients, the bone metastasis was ipsilateral to the involved kidney, in 4 contralateral, and in 11 the non-axial metastases were bilateral. The difference be-tween ipsi- and contralateral was significant at $p<0.01$. A good explanation of the homolaterality is the mechanism of spread along the homolateral plexus of Batson. We are not aware of similar data in other reports, but this is clearly a matter that should be examined further. The same author also made a statistical study of the distribution of metastases within the spine. Of the 93 metastatic sites within 40 patients, nearly half were in the lumbar vertebrae (fig. 11.8).

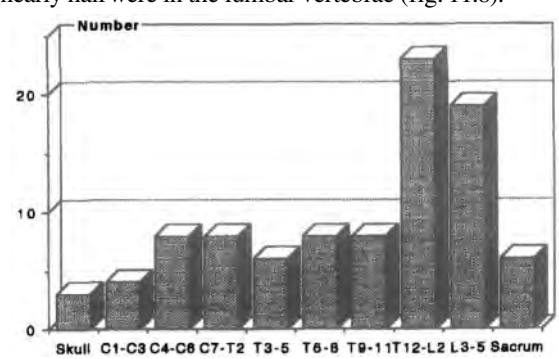

Fig. 11.8 - Renal cell cancer: Distribution of bone metastases within the spine. Drawn from data of Arkless.

In spite of the significant number of spinal metastases, spinal cord compression has hardly ever been specifically studied for renal cancer.Two cases were discussed by Fritzsche et al., one at T4 and one at L1-L3.

Acral bone metastases have rarely been reported. We collected some cases in table 11.34.

A review by Kerin in 1987 disclosed 14 cases from

renal cell cancer. We found in the literature about as many cases in the hand as in the foot, but much more cases from the left kidney. In the hand, the phalanges are most frequently involved, but in the foot the metatarsal and calcaneus. It should occur more in male, in a ratio of 4 to 1. Several are revealing metastases.
Goldman et al. have reported on a F72 presenting with pain in the right ankle (calcaneum). She was shown to have a left kidney cancer. Subsequently, she developed new metastases in the left navicular, the right second metastarsal and the distal end of the right tibia.

Table 11.34 - Renal Cell Carcinoma
Acral Metastases- Cases reported and available

Author	Patient	Kidney	Site	Interval
Anderson 1968	M56	Le	Ri.great toe	Reveal
Coffman 1975	M62	Ri	Left index finger	Reveal
Potter 1991	M69	??	Left fifth toe	Reveal
Troncoso 1991	M53	Ri	Le index	2 yrs
Troncoso 1991	M62	Le	Le 2nd toe	1 yr
Bibi 1993 (')	M60	Ri	Ri.little finger	3 yrs
Sidhu 1994	M71	Le	Le little finger	2 yrs
Adegboyega '99	F60	Ri	Ri middle finger	Reveal
Weber 1999	M83	Le	Ri.Patella	Reveal

(') concerns soft tissue.

A particular and rare form of bone metastasis is the pulsating form. The abundant vascularity of the metastases is a predisposing factor for shunting between arterial and venous resulting in a pulsating tumor. Several cases have been reported and reviewed by Estrera et al. We are not aware of reports since 1981.

Another unusual presentation is the monarthritis. A man (M57) presented with pain in left ankle and a woman (F58) with pronounced hip pain. In both instances cytology led to further investigations which revealed a kidney malignancy (Chakravarty et al.).

Cutaneous Metastases

Renal cell carcinoma is well known for the various types of presentation of skin metastases. Descriptions such as nodular, multinodular, hemorrahagic, plaque-like, zoster-iform and tumorous are usual in the literature. Many indeed masquerade as other common skin lesions.

From the few series reported, a preponderance of the upper half of the body, particularly the face and scalp should be noted. According to a recent review by Koga et al., 40% of the 75 cases were at the trunk, 10% at the extremities and 25% at the scalp. The lesion was solitary in 75%, and as type 1 presentation in 24% (see also fig.7.3).

A Sister Joseph nodule or umbilical metastasis was the revealing sign of a large right renal mass in a F45 (Chen et al.).

Metastases to Muscles

Muscular metastases will come to the attention as a swelling and/or pain, and are frequently described in renal cell carcinoma (table 11.36).
The reported data show that 6 of the 14 were in the lower limb, with an additional 2 in the psoas and another in the abdominal wall. Only one case was a revealing metastasis, and in 7 the interval was longer than 10 years. One possible explanation to this is that metastases in the muscle grow slowly, so that it will appear only in long-term survivors.

Table 11.36 - Renal Cell Carcinoma
Metastases in the Muscle - Literature reports

Author	Pat.	Kidney	Site of M	Interval
Kradjian 1965	F66	Ri.	Ri.M.Rectus Abd.	31 yrs
Chandler '79	M62	Le.	Ri.Biceps Brach.	Reveal.
Karakousis'83	M63	Ri.	Ri.Vastus med.	5 yrs
Stener 1984	M55	??	Left thigh	33 mo
	M46	??	Left thigh	16 yrs
Alexiou 1984	M74	Ri	Left arm	Reveal
Merimsky '90	M69	Le	Thigh, gluteus	1 yr
Fullarton '91	F43	Ri.	Le.Deltoid	23 yrs
Ruiz 1991	F63	??	Thigh - Brachialis	16 yrs
Munk 1992	M57	Ri	Ri.M.Trapezius	10 mo
DiTonno '93	M55	Ri.	Le.M.Gluteus Mx	12 yrs
Linn 1996	M58	Ri.	Le.Psoas	14 yrs
Nakagawa'96	M57	??	Le.Masseter (')	4 yrs
Gal 1997	M49	Le	Ri.Masseter	Reveal
Rothfuss '98	F72	Ri.	Li. Gastrocnemius	20 yrs
Pfitzenm.'99	M46	Ri.	Le.Psoas	14 yrs

(') previously a left temporal brain metastasis

Non-Regional Lymph Node Metasases

Mediastinohilar lymph nodes have been discussed along with the thoracal metastases.
Supraclavicular metastases have been mentioned as first sign, also during the evolution. They no doubt originate from lymphatic reflux at the entrance of the thoracic duct into the subclavian vein.
Rare cases of axillary lymph node metastases have been reported during the evolution. Progressive obstruction of the central lymphatic pathways may result in a subtegumental flow in the abdomen, with a flow directly to the axillary region.

Overall Lessons

When urologic symptoms present, diagnosing a renal tumor is relatively easy.
When its appearance is by a metastasis, the diagnosis is much more difficult and depends on the clinical perspicacity of the first specialist consulted and on the pathologist confronted with a histology unusual for the region or organ biopsied.
If metastases appear several years after the first treatment, the patients, considering that they were cured of the cancer, will frequently omit mention of the previous treatment, delaying the definite diagnosis.
We would like to suggest that in case reports, the side

of the renal tumors should always be mentioned. Furthermore, as numerous patients are in institutional data-bases,it would be easy to retrieve the metastatic pattern, the sequential occurrence and to correlate these with the gender of the patients, the side of the renal tumor and many other features, in order to examine the possible correlations further.

METASTASES from WILMS' TUMOR

Wilms' tumor or nephroblastoma is a rare renal embryonal tumor, but the most common abdominal tumor, in young children.
The incidence of metastases is approximately 10%, with the lymph nodes, the lungs, the liver and bone as most common site.

According to Rao et al., the less common metastases to bone and brain are associated with specific histological subtypes.

Abdominal metastases

Although not uncommon in Wilms' tumor patients, only Slasky et al. have studied the abdominal metastases. At CT the usual signs of metastatic involvement were observed as solid masses under the diaphragm, on the mesentery and peritoneum, cake-like masses in the omentum, and in most of the patients so-called drop metastases in the pelvis. The various masses are inhomogenous, with zones of necrosis, and have a lobular irregular or rounded, sometimes infiltrative, configuration.

Metastases to the Regional Lymph Nodes

Data on precise incidence and location are to our knowledge not available.
A few patients have been mentioned as having developed mediastinal and supraclavicular nodes.

Metastases to the Central Nervous System

Intracranial metastases are very rare. Reporting a particular case, presenting with intracranial hemorrhage, Takamiya et al. reviewed the literature in 1985 and found 14 reported cases. Some were old reports and other seemed to have been reported within unaccessible reports. In the list reported, we saw that in 5 of the nine cases it was a single metastasis and located in the frontal region. Six patients had multiple metastases and one was located in the brain stem.
In the UKW-1&2 trials enrolling 834 patients, 7 patients developed CNS metastases (Lowis et al.). From a literature review, they retrieved 23 other reported cases. Data on site were lacking in 6, while the metastases were multiple in 6 and frontal in 4. There was one in the brainstem and one in the cerebellum.

Intraspinal extradural metastases without bone involvement and sometimes solitary have been reported. Two cases were discussed by Cohn et al., who found 27 additional patients in the literature, of whom 16 from the National Data Base. The site or level is however, not available from their data.
A review of Darendeliler et al. on 16 patients shows that most were in the thoracal region.

Bone metastases

In contrast to neuroblastoma, bone metastases in Wilms' tumor patients are rare. Some previous series have been reported, but modern pathology has shown that these patients with 'bone metastasizing renal tumor in childhood' (BMRTC) constituted a distinct pathology, now regarded as clear-cell sarcoma of the kidney.

The incidence of bone metastases amounts to 60% in BMRTC or clear cell sarcoma, while it is only 2% in classical Wilms' (Gururangan et al.). The lesions are often multiple, rarely solitary. A very few have bone metastases at presentation (Meister et al.).
An important report in this regard was of Marsden et al. (1980). They clearly showed a site difference between the metastases (table 11.37).
There is a clear difference between both groups: in BMRTC skull and the skeleton of the upper body is involved in 90%, while in true Wilms' tumor it concerns the axial skeleton. In both groups, the bone metastases are prominently osteolytic and very destructive of both cancellous and compact bone.

Table 11.37 - Renal Tumors in Childhood
Bone metastases according to Histology
Modified from Marsden et al.

Site	BMRTC (') N=23	Wilms' N=18
Skull	13	3
Orbit	1	--
Humerus	2	1
Radius	1	--
Scapula	2	3
Ribs	2	2
Cerv.Spine	2	--
Spine	1	9
Shoulder	2	--
Clavicle	1	--
Sternum	1	--
Wrist	1	--
Femur	6	1
Tibia	1	--
Pelvis	1	4

(')bone metastasizing renal tumor in childhood

Spinal cord compression has been reported in Wilms' tumor in two ways, either as subarachnoidal mass (intradural), or due to involvement of the spine, with direct extension to the epidural space. Reporting on two cases, Ebb et al. found 4 cases in the National (USA) Wilms' Tumor Study data base (3067 patients)

and two others in the literature (1992). Two other cases were reported by Benouachane et al. In both patients, a vertebral osteolysis was associated with an epidural mass compressing the spinal cord.

Pulmonary Metastases

In spite of numerous protocols and trials of treatments of pulmonary metastases, their reports do not contain any data on site distribution, size or multiplicity. The report of Schlienger et al., dating back to 1974 mentions bilaterality in 48% of the 116 patients. Unilaterality was observed in 40% and in 11% nodules or effusion associated with atelectasia was seen. In one quarter, the metastases were present at diagnosis.
A recent report of Wootton-Georges et al. on 83 patients reveals that pulmonary nodules were observed in 12 or 14.4% of the patients at presentation.

Pleural metastases, which are generally hemorrhagic, are uncommon (Betkerur et al.). Data on incidence and morphology are lacking.

Cardiac involvement

The main form of cardiac involvement is the tumor thrombus from the vena cava inferior up to the right heart. This seems not to be uncommon, as in the 1,865 evaluable patients registered at the NWTS, 77 or 4.1% had a caval or atrial thrombus (Ritchey et al.). The level was infrahepatic in 61%, with 21 % intra-atrial. Ultrasonography plays a major role in detection, but many were detected only at surgery. More extensive preoperative studies will eliminate this unexpected problem.

Unusual Metastases

One patient (Ml) was reported as presenting simultaneously with a left kidney tumor and a left testicular metastasis.
Two cases have been reported by Zakowski where sudden death was caused by a tumor embolus in the right main pulmonary artery, metastatic from an unknown right Wilms' tumor. One also had a large tumor embolus in the right internal carotid.

Movassaghi et al. have reported on a 3.5 year old girl developing metastases to the bone marrow, the parotid gland, the tonsil, pancreas, liver, kidney retroperitoneal and mediastinal lymph nodes, simultaneously with several bone metastases.

An 8-year old boy presented with difficulty in breathing and bleeding from the nose, one year after surgery for a left-sided Wilms' tumor. There was an extensive tumoral mass filling the nasopharynx and coming down towards the tongue (Rao et al.).

Orbital metastases are rare. Fratkin et al. reported on a 2.5 year old boy developing metastasis at that site, one year after first treatment, and found two other reported.
Muscle metastases have been reported in a few cases. Three and a half years after first treatment a metastasis in the left gastrocnemius occurred in a 9 year old girl (Rao et al.).

Urologic metastases, either in the ureter, urinary bladder (Pagano et al.) or in the urethra (Lowe et al;) were the subject of case reports.
One patient reported by Fay et al., developed mandibular, pulmonary and supraclavi-cular nodal metastases 14 years after treatment. The patient rapidly deteriorated and at autopsy metastases were present almost 'everywhere'.

METASTASES from TUMORS of the RENAL PELVIS

Tumors of the renal pelvis are less common than renal cell cancers. Nevertheless several series have been reported. In almost all series distant metastases are mentioned but the sites are not specified.
A few case reports have appeared in the literature (table 11.38).

Table 11.38 - Transitional Cancer of the Renal Pelvis Distant Metastases in the Literature

Author	Pat.	Site of Metastasis	Interval
Lisbona 1972	M65	M.psoas (bilateral)	5 yrs
Atta 1983	F50	Eye Choroid	3 yrs
Kabalin 1990	M53	Pulmo Brain mult.	1year
Hsiu 1991	F48	Ri.Ovary	simult.
Ando 1994	M67	Nodes Axill.-SC	
		Skin of trunk	3 yrs

The skin metastases described in the case of Ando et al. were of the zosteriform type. This type has also been reported in cancer of the urinary bladder.
As reported by Kabalin et al. brain metastases are rare in transitional cancer. They found only one other case reported.
While a number of transitional cell cancers metastatic to the ovary have been reported, the case published by Hsiu et al. is the only one reported as originating from a renal pelvis tumor.

Reviewing 11 literature cases of adenocarcinoma of the renal pelvis, Ashhley et al. mention three patients having died of widespread metastases. They were in the liver, the lung, and in lymph nodes without more specification. Another review on 15 cases with mucin-secreting adenocarcinoma of the renal pelvis by Murphy et al. mentions metastases in the abdominal nodes, the abdominal wall, adrenals, peritoneal carcinomatosis and cervical nodes in 5 of the patients.

A 'track-recurrence' after laparoscopic resection of a tumor in the renal pelvis was reported by Ahmed et al. This was a iatrogenic metastasis.

METASTASES from CANCER of the URETER

Cancer of the ureter is an uncommon cancer. Before the CT era it was somewhat difficult to diagnosis, even though IV-pyelography provided good images. At the current time, the extent and degree of invasiveness can be evaluated much better before surgery.

This cancer originates in the mucosa, from where it will invade through the wall, grow into the lumen and spread longitudinally. It will invade the peri-ureteral, the prevertebral and para aortic lymph nodes in the mode as described for renal or testicular cancer.

Distant metastases have been reported in a high number, but the few reports contain few details about site distribution.
The incidence of distant metastases is difficult to estimate. In his seminal multi-center study dating back to 1974, Mazeman quoted a figure of 17% of 1078 patients, including 60% tumors of the renal pelvis. 75% of the metastases occurred within two years.

Autopsy data have been provided by Batata et al. on 12 patients (table 11.39).
The table shows the extensive intra-abdominal spread that can occur, but also spread to many other organs. It would appear to be a very aggressive cancer as half of the patients had distant metastases. There were even axillary and cervical metastatic lymph nodes.

Holtz mentions two autopsies. Both had metastases to lymph nodes, lungs, liver and vertebrae. One had metastases to the thyroid and the spermatic cord. Several nodules in the right spermatic cord, homolateral to the ureteral primary were observed in a case (M65) one year after first surgery (Komeda et al.).

Table 11.39 - Cancer of the Ureter
Distant Metastases (N=12)
Data of Batata et al. 1975

Abdominal		Extra-Abdominal	
Pelvic nodes	12	Bone	5
Para-aortic nodes	10	Lung	4
Liver	9	Inguinal nodes	3
Iliac vessels	7	Neck nodes	3
Bowel	7	Breast	2
Peritoneum	6	Pleura	2
M.Iliopsoas	3	Vagina	2
Abdominal wall	2	Axillary nodes	1
Uterus	2		
Ovary	2		
Adrenal	1		

METASTASES from CANCER of the URINARY BLADDER

Cancer of the urinary bladder is an insidious locally growing tumor, progressively infiltrating all layers and invading the perivesical tissue. From then on cells will be picked up by lymph flow in the vessels or in the venous system who will eventually generate new distant metastases.

Metastatic Pattern

The metastatic pattern of bladder cancer has not been extensively studied. Many articles concerning unusual locations of metastases from this particular cancer have been published. It should be remembered that bladder cancer is a malignancy of a transitional cell epithelium, probably quite different from the other epithelia as far as biologic features concern.

Apart from local spread and eventually contiguous invasion, there is a prominent lymphatic involvement in bladder cancer. This involvement is not only local but can extend retroperitoneally and up to the mediastinum and higher.

Table 11.40 - Cancer of the Urinary Bladder
Metastatic pattern from autopsy data

Site	Melicow N=125	Friedell N=31 (‘)	Sulmoni N=91(°)	Babaian N=107(“
Abdomino-Pelvic				
Regional nodes	27	16	--	25%
Liver	21	5	36	38%
Adrenal	9	3	3	21
Kidney	7	1	4	7
Pancreas	2	1	--	7
Ureter	--	1	--	--
Spleen	--	--	1	7
Intestine	10	--	--	13
Uterus	--	--	--	4(*)
Ovary	--	--	--	4(*)
Prostate	--	--	--	4(*)
Testis	--	--	--	1(*)
Supra-Diaphragmatic				
Lung	22	7	23	36%
Heart	8	1	--	8
Thyroid	--	1	1	--
Bone	19	5	20	27
Brain	2	--	3	7
Skin	--	--	1	--
Meninges	--	--	--	5

(‘) all untreated cases, metastases found in 20 cases.
(°) of 432 treated cases
(“) all patients dying with metastases
(*) resp. of female and male patients.

The general pattern of metastasis at death can be gauged according to the data of Friedel. Of 31 patients, 20 had pelvic extension, of whom 13 also had distant metastases. Of the 11 without extension, 7 had

distant metastases, bringing the total number to 20.

Autopsy studies

A few studies have reported the repartition of distant metastasis in autopsied patients. The data are not easy to compare, as the population examined is different and the data reported in different ways. We compare four series in table 11.40.
The oldest known is that of Melicow. Later Friedell reported on untreated patients, but when compared with the other series, the pattern does not differ very much from treated patients. A series reported by Kishi et al., showed essentially the same pattern. They only mention 15.2% vaginal recurrences, a site not mentioned in the other series. Several of the patients studied had been subjected to cystectomy, so that at death a vaginal recurrence was not impossible. Melicow also found 3 diaphragmatic metastases, 2 in the gallbladder, and 18 retroperitoneal nodes in his series of 125 consecutive autopsies.

Table 11.41 - Cancer of the Urinary Bladder
Distant Metastases at autopsy
(Transitional Cell Cancer N=214)
Data of Wallmeroth et al. 1999

Pelvic		Supra-Diaphragmatic	
Uterus	1%	Lung	45%
Vagina	1	Pleura	15
Ovary	1	Heart	6
Penis	1	Brain	4
		Thyroid	2
Bone	33	Tonsil	0.5
Skin	0.5	Breast	0.5
		Dura	2
Abdomen			
Liver	48%	Stomach	3%
Peritoneum	18	Gallbladder	2
Kidney	14	Spleen	5
Adrenal	13	Pancreas	6
Intestine	12		

Recently, an extensive autopsy study involving 367 patients was reported, of whom 251 or 68% had any metastases. Table 11.41 the results obtained in the 214 patients with transitional cell cancers.

Clinical Study

The study by Sengelov et al. has provided interesting data. They examined the influence of several features on the incidence and distribution of metastases.

- Local recurrences and metastases in the lung were diagnosed significantly earlier than other metastases.
- Multiple sites were involved in more than half of the patients (with recurrence or metastases).
- The most common site of (metastatic) recurrences were: local 65%, bone 35%, lymph nodes 26% and lung 20%.
- Histology type, grade, and location within the bladder exhibited the same pattern of distant metastases.
- Patients younger than 60 years had more distant metastases, most pronounced for bone.
- Local recurrence was frequently accompanied by distant metastases.

Direct Extension

At autopsy of 31 cases, direct extension towards pelvic organs was found in 20 cases (table 11.41). Extension towards the prostate is a noteworthy feature.
Extension within the pelvic cavity with compression and obstruction of the ureters or the rectal ampulla is not uncommon (fig. 11.9).
Spread towards the ureter has been described even up to its cranial end. Implantation metastases is one explanation, but in our opinion field cancerisation is more likely (Viville), or peri-ureteral spread.

Table 11.41 - Cancer of the Urinary Bladder
Pelvic Extension at autopsy (Literature data)

	Friedell N=31(')	Melicow N=88 autopsies
Prostate	11	21
Seminal vesicles	8	15
Ureter	1	--
Pararectal tissue	1	--
Rectum	2	15 (incl.ileum,colon)
Paravesical	1	32
Cervix	1	4
Vagina	1	1
Vessels	1	--

Fig. 11.9 - Artist's view of the contiguous extension of a bladder tumor towards the rectum with obstruction

Lymp Node Metastases

The UICC nomenclature of the staging of lymph node metastases is somewhat 'simplified'.
The regional lymph nodes are the pelvic nodes below the bifurcation of the common iliac arteries
The juxtaregional lymph nodes are the inguinal, the common iliac and the para-aortic lymph nodes
N1: evidence of involvement of a single homolateral regional lymph node;
N2: involvement of contralateral or bilateral or mul-

tiple regional lymph nodes;
N3: Involvement of fixed regional lymph nodes, which means a fixed mass on the pelvic wall with a free space between it and the primary;
N4: involvement of juxtaregional lymph nodes.

Table 11.42 - Cancer of the Urinary Bladder
Lymph nodes involved (20% of 662 patients)
Data of Smith et al. 1981

Obturator	99 (74% of the 'positive' patients)
External Iliac	87 (65%)
Hypogastric	23 (17%)
Perivesical	21 (16%)
Common Iliac	25 (19%)

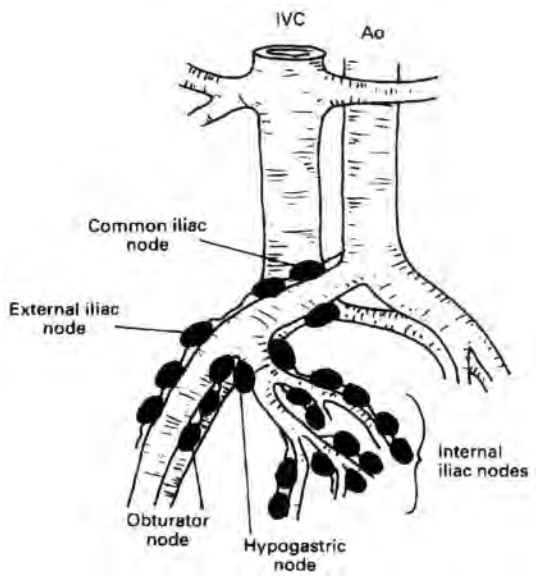

Fig. 11.10 - The different lymph node stations tributary to a cancer of the bladder (Husband, with permission)

Table 11.43 - Cancer of the Urinary Bladder
Lymph Node Metastatic pattern from autopsy data

	Sulmoni N=91	Kishi N=87	Walmeroth N=214(')
Iliacal	36	9.2%	Pelv.74%
Presacral	4	--	--
Inguinal	13	4.6	--
Para-aortic	30 Lumb	11.5	62%
Celiac	--	30%	--
Portal	2	--	--
Pancreatico-Duod	5	6.9	Abd.32%
Mesenterial	4	11.5	--
Tracheobronchial	7	8.0	--
Mediast.Poster.	--	2.3	26%
Infra-Supraclav	3	13.5%	--
Cervical	2	--	4%
Axillary	1	--	--
Any Node			84%

(') only TCC

At radical cystectomy with bilateral lymph node dissection in 662 patients, Smith et al. observed a relatively high incidence of involved lymph nodes. Pathological evidence was found in 134 patients or 20%. The distribution of positive nodes according to station is in table 11.42.

Distant nodes were reported in 50% of 107 patients autopsied by Babaian et al. Comparative data on lymph node metastases from three reports are in table 11.43.

The latest autopsy study by Wallmeroth et al. mentions the presence of any lymph node metastases in 215 of the 308 patients with TCC, or 69%. Of these patients, 92% had regional (perivesical or pelvic), 72% in the retroperitoneal space and 35% in the abdominal lymph nodes. Thoracic nodes were the only nodes involved in 3 patients, but all also had lung metastases, probably the source of these nodes. Cervical nodes were also always associated with other metastatic nodes.

Distant Metastases

The incidence of distant metastases, except for liver, lungs and bones, is low. These three probably have different pathways. Liver metastases from urinary bladder cancer is almost not addressed in the literature.

Bone Metastases

The pattern of bone metastases at autopsy has been reported by Kishi et al. (table 11.44). The majority are at the spine, so that venous seeding along the prevertebral plexus of Batson, is the most probable pathway.

Table 11.44 - Cancer of the Urinary Bladder
Bone Metastatic pattern from autopsy (N=87)
Data of Kishi

Bones	24.1%
Thoracic Vertebrae	4.6%
Lumbar-Sacral	18.4%

Sengelov et al. found 157 bony metastatic sites in 85 patients or 20% of the 423 patients studied. The distribution is shown in table 11.45, compared with the data of Melicov.

Table 11. 45- Cancer of the Urinary Bladder
Bone Metastatic pattern

	Melicow (") 19/125	Sengelov(') N=85
Skull	--	2%
Mandible	--	1
Clavicle	--	2
Sternum	1	1
Spine	11	40%
Pelvis	8	26%
Ribs	5	10
Humerus	--	5
Femur	1	10
Tibia	--	3

(") 125 consecutive autopsies
(') clinical follow-up

These data show a distribution similar to that of the other pelvic tumors, with a majority within the pelvis and spine, but quite a number of femoral location, which may be explained by some venous reflux.
A radiological study of 75 patients disclosed bone metastases in 23 or 28%. The image was osteolytic in 11, osteoblastic in 6 and mixed in 4. Bone metastases were visible only by scintigraphy in 3 patients (Goldman et al.).

Hoffman reports an incidence of 11 cases out of 59 or 18.6%. Except one at the clavicle, no particular site is mentioned. In a report on 8 cases, one metastasis in the pubis as a revealing metastasis is reported by Kretschmer et al. Seven patients with femoral metastases from a bladder cancer were treated by intramedullary nailing and reported by Katzner et al.
Engelstein et al. have reported on a M62 presenting with headache. A skull film revealed a radiolucent lesion, and a biopsy showed a transitional cell carcinoma. Other bone metastases were present and cystoscopy and biopsy confirmed the primary.
The rare site of metastasis in the temporal bone was reported in a 80 year old man complaining of recent hearing loss (Saldanha et al.).

A metastasis in the talus is reported by Dunnick et al. and one by Dumontet et al. Osteolysis of several tarsal bones occurred 13 years after treatment of a superficial bladder cancer in a M83 (Sarup et al.). Quadri et al. previously reported one case (M70) with metastasis to the distal end of the tibia and one (F76) in the talus.
Hand metastases have been reported. Multiple lumps on the back of the right hand were the first sign of a metastatic urinary bladder cancer in a M65 (Heymans et al.). Walsh et al. have reported on a M46 with metastases in the right index associated with many other metastatic sites.

Lung Metastases

In all autopsy reports, the frequency of lung metastases was second highest to the frequency in liver, up to 35% of patients with metastases.
There is a paucity of data on lung metastases in bladder cancer. In a radiological survey of 51 patients by Goldberg et al., a lung abnormality was detected in 23 of 380 radiographs, a peculiar way of reporting incidence. Multiple nodules were present in 13, a solitary in 7, an infiltrate in 5 and a so-called Pancoast tumor in one.

Cavitating lung metastases were reported in two patients of a file of 343 urinary bladder cancer patients (Angulo et al.). Four other cases have been reported, two each by Rovirosa et al. and Alexander et al. This type of lung metastasis should be sought in the files, as it would appear not to be particularly rare in bladder cancer.
One patient with a late biopsy-proven lung metastasis occurring 25 years after surgery was reported by Seymour et al..

Brain Metastases

Although occurring in less than 5% of the patients at autopsy, several cases have been reported. Remarkable is that a large majority are single, even solitary. A literature review by Anderson et al. disclosed 26 cases reported up to 1992, of which 19 or 73% were solitary. Of the 19 reported by Rosenstein et al., 13 were single.
A higher incidence has been noted in chemotherapy treated patients. Of 50 patients treated only by chemotherapy for advanced cancers, 8 or 16% experienced brain metastases during follow-up. Six had single metastases.

Table 11.46 - Cancer of the Urinary Bladder
Cases with Leptomeningeal Carcinomatosis
Literature Review by the author

Author	Pat	Stage(')	Interval
Wieczorek 1964	no data		
Hust 1982	M54	T1	no data
Hust 1982	F60	Tx	no data
Mandell 1985	M59	T2	22 mo
Hussein 1989	M60	'D'	10 mo
Bishop 1990	M60	T1 (?)	--
Bishop 1990	M55	B2 (?)	--
Raghavan 1991	M42	T1	16 mo
Eng 1993	M71	T2	10 mo
Eng 1993	M64	T4	24 mo
Hasbini 1997	M63	T3	6 mo
Stastny 1997	M53	T3	24 mo
Statsny 1997	F60	T2 (?)	12 mo

(') Stage at diagnosis

In general, there is no site preference within the brain.
Two cases have been reported where the brain metastasis was the first symptom (Angulo et al.; Le Chevalier et al.).
Two patients have been reported with a cerebellar metastasis (Shamdas et al.; Steinfeld et al.). Of the four cases reported by Kabalin et al., two were cerebellar. Findler et al. reported on a man who presented with transient global amnesia. A CT disclosed a solitary metastasis in the right posterior thalamic region, two years after diagnosis of the primary.
A number of reports with neurosurgically treated patients have been published, all concerning single or solitary lesions. Cases with multiple metastases are probably underreported as they are not surgically treated.
On the other hand, leptomeningeal carcinomatosis has also been reported in several cases (table 11.46). All patients had chemotherapy either adjuvant or as unique treatment for advanced tumors. All except 2 of the 13 cases were men.

Ophthalmic Metastases

These are rare in bladder cancer. Only a few cases have

been published, with a relatively large proportion in the orbit (table 11.47). Several were type 1 metastases. A case of metastases at the conjunc-tival side of the upper eyelid was reported by Hollander et al.
Only a few choroidal metastases were observed or at least published.

Table 11.47 - Cancer of the Bladder Ophthalmic Metastases.

Author	Patient	Site	Interval
Orbit			
Smiley 1965	M75	Le.orbit	Revealing
Kraus 1982	F64	Orbit	15 mo
Angulo 1991	M61	Orbit	11 mo
Felip 1991	M58	Orbit	Revealing
Felip 1991 (2)	M62	Le.Orbit	3 yrs
Nieder 1995	F67	Orbit (with brainstem)	
Choroid			
Resnick 1975 (1)	M46	Ri. Choroid	1 mo
Resnick 1975 (2)	M51	Ri. Choroid	14 mo
Cieplinski 1982	M57	Bil. Choroid	1 yr
Peer 1984 (')	M69	Choroid	2 yrs
Hugkulstone'94	M45	Bil. choroid	Revealing

(') at the ureter.

Skin Metastases

There are a large number of reports concerning skin metastases from bladder cancer. A 1968 literature review by Hollander et al. could retrieve 20 cases, of which only 2 were female patients, probably reflecting the gender difference observed in primary bladder cancer.
Skin metastases of bladder cancer are usually multiple all over the trunk, but also over the lower extremities. This is very unusual, as skin metastases of other cancers are usually solitary or occur in low numbers.
Since 1968, only 20 reports have appeared and these have concerned one or on rare occasions, two patients, but almost all had multiple lesions. Some were a type 1 presentation (Schwartz et al.; Vidmar et al.).
The case reported by Schwarz et al. was probably an ulcerated inguinal node metastasis. Another case reported as zoster sine herpe was most probably a cutaneous infiltration from an underlying thoracic wall and intercostal metastatic infiltration (Jaworsky et al.).

Umbilical metastases have also been reported (Edoute et al.).

Involvement of the anterior abdominal wall may possibly occur as an extension of advanced bladder cancer, but has also been described as a recurrence after any surgery (Bracken et al.).

Genital Metastases

Metastases to the genitalia must first be differentiated from a contiguous invasion. Tthey can also be caused by venous or lymphatic obstruction with flow reversal.
Nevertheless, such metastases have rarely been reported. Vaginal, vulvar and clitoral (twice) have been described, all in relatively old women.
An ovarian metastasis was disclosed at surgery in a T1 bladder cancer (Kardar et al.). Eleven other cases should have been reported, of which 3 with a superficial cancer. Two other cases have been published. In a young woman, an ovarian metastasis appear-ed two years after a radical cystectomy (Groutz et al.).
Epstein has reported a patient presenting with post-menopausal bleeding 6 months after total cystectomy. Curetage revealed metastatic transitional-cell cancer cells. We are not aware of any other case, or of metastases to the cervix uteri.

In men, rare cases of metastases to the penis, the testicles and spermatic cord have been reported. The most frequent site is the penis. Three such patients, of whom one at presentation, were reported by Ucar et al. They can all be explained in terms of a lymphatic reflux.
One penile metastasis occurred in a bladder cancer patient, 4 years after a successful heart transplantation (Maier et al.).
Invasion of the prostate is common, but not to be considered true metastasis.

Other Metastases

A 65-year-old man was found to have an extensive soft-tissue swelling at the dorsum of the hand, in whom a biopsy revealed a transitional cell cancer. At autopsy, a vesical tumor was confirmed (Heymans et al.).

Some Head-and-Neck metastases have also been reported: one year after surgery, a metastasis in the submandibular gland (Edwab et al.), one in the maxilla (Cohen et al.) and one patient with a metastasis at the mandible (Treggiden). A rare metastasis to the tongue (lateral border) was found simultaneously with the diagnosis of a T3 bladder cancer (Koper et al.). We are aware of 6 cases metastatic to the mandible and 3 to the maxilla (Cardone et al.).
We were recently consulted about a patient (M48) whose first symptom was a long-standing pain at the thyroid cartilage. After several negative imaging, at last a swelling was noted and turned out to be a metastatic transitional carcinoma.

A few cases have been reported with metastases in the M.Iliopsoas, probably due to invasion from metastatic nodes (Natour et al. and Masters et al. (2 cases)). A man with right flank and groin pain was diagnosed as having a psoas abcess, but further investigations demonstrated an advanced bladder cancer (Yap et al.).

Two cases of esophageal metastases have been described, both during follow-up (Dy et al. and Jung et al.).
Peritoneal carcinomatosis was reported by Pevarski et al. in two patients, both metachronous after diagnosis,

one of them having had a radical cystectomy. We are not aware of other reports of this rare metastasis from bladder cancer.

The rare situation of spontaneous rupture of the spleen due to metastasis was reported in a patient (M84) five days after TUR for a mucous-producing signet-ring cell carcinoma (Rüther et al.).

Other cases that should be mentioned involved cardiac metastasis at the right ventricle within the endocard (Clemente et al.) and one presenting with a malignant pericarditis as revea-ling and sole symptom of a bladder cancer (Fabozzi et al.). A polypoid pedunculated tumoral metastases in the pericard was diagnosed after paracentesis of a cardiac tamponade in a man treated three years previously (Gibbs et al.).
A very rare case of pleural metastasis was reported by Nieto-Llanos et al.
A double metastasis in the breast occurred two years after cystectomy and chemotherapy in a 57-year-old woman (Belton et al.). Only two other cases have been reported. A little more than 2 years after cystectomy, a 69-year-old black man presented with a mass in the left breast, at biopsy confirmed as transitional cell carcinoma (Truesdale et al.).

Overall Lesson

Cancer of the bladder is a tumor which will remain for a long time within the pelvis and which has a low incidence of distant metastases, except in the liver and lungs. Distant metastases in other sites are rare and involve uncommon sites.

METASTASES from URACHAL CARCINOMA

Urachal carcinoma arises in the extraperitoneal space between bladder and abdominal wall, from an embryologic remnant connecting the umbilicus to the apex of the urinary bladder. It is a rare site for cancer. Nevertheless, several malignant cases have been reported with distant metastases.
A review in 1983 could retrieve 72 cases with reported metastases (Kakizoe et al.) (table 11.48).

Table 11.48 - Carcinoma of the Urachus
Distant Metastases - Literature Review (N=72)
Data of Kakizoe et al. 1983

Lymph nodes	30.5%	Liver	13.8
Lungs	27.7	Bone	12.5
Peritoneum	19.4	Small bowel	11.1
Omentum	18.0	Others	12.5
Mesentery	15.2		

The tumor probably extends by local invasion of the abdominal wall and the peritoneum with further progression towards the mesentery, the omentum and the intestine. To what extent this differs from a contiguous invasion is not clear from the data reported.
The rarity of this primary does not permit any conclusion about a metastatic pattern, but local involvement of abdominal wall and peritoneal content is the dominant clinical picture. A type 1 presentation will make the diagnosis relatively difficult.
Recently, a patient was reported (M35) where a painless hematuria disclosed an extensive urachal carcinoma, with infiltration up to the distal face of the diaphragm (Loggie et al.).

Young has reported on one case with ovarian metastases resected at the first operation, but first diagnosed as a primary mucinous ovarian carcinoma.
There have been two reports of brain metastases. A type 1 presentation with parieto-occipital metastasis (Fujiwara et al.) and one in a women of 22 years of age, with a metastasis in the temporo-parietal lobe, 7 months after surgery (Tewari et al.).
A case of widespread bone metastases one year after surgery was reported by Mohanti et al., while additionally to bone and skin metastases, orbital involvement in addition was observed in a young women of 28 years of age (Giordano et al.).

METASTASES from CANCER of the PROSTATE

Cancer of the prostate has, compared to the malignant tumors of the other male urogenital organs, a completely different metastatic behavior.

Hidden deep within the pelvis, but nevertheless within 'finger-reach', it first develops locally and then spreads towards the pelvic lymph nodes. The prostate is also in close contact with the pelvic venous plexuses draining either towards Batson's pathway or towards the general circulation. This results in a dual pattern of spread, where either one or both pathways occurs, to whom the lymphatic pathway must be added.

Autopsy Data - Overall Pattern

A number of studies have reported autopsy data of prostate cancer patients.
In a report dealing on 144 patients, the cancer was limited to the prostate and without metastases in 82 patients, leaving 62 patients for study (Lamothe et al. 1966). As their data are given in a particular way, we have modified them to refer for 44 patients (table 11.49).
Despite the low number of the patients, the data give some idea of the high proportion of lymph node metastases on one hand and bone involvement on the other hand. The high rate of bladder involvement must be considered mainly contiguous invasion.

Table 11. 49 - Cancer of the Prostate
Metastatic Spread - Autopsy data (N=44)
Modified from Lamothe et al.

Pelvic		Supra-Diaphragmatic	
Lymph node	86.3%	Bone	79.5%
Urinary Bladder	68.1	Lung	22.7
Seminal Vesicle	13.6	Thyroid	9.1
Testicle	2.2	Breast	6.8
Penis	2.2	Brain	6.8
Vas Deferens	2.2	Pleura	4.5
		Skin	2.2
Abdomen		Mediastinum	2.2
Liver	32.0	Pericardium	2.2
Kidney	18.1	Diaphragm	2.2
Pancreas	2.2		
Ureter	6.8		
GIT	18.1		
Adrenal	13.6		
Peritoneum	6.8		

The authors compared their data which mainly related to black patients, with the data of the Memorial Hospital, a predominantly white series. Black patients had proportionally more pelvic lymph nodes, while in the white, there were substantially more retroperitoneal lymph node metastases. White patients had also fewer bone metastases than black patients. This indicates some racial factors may be involved, but further data are apparently lacking.

Correlation with the histology type yields as one would expect a high number in poorly differentiated cancers and tumors with transitional or squamous cell histology (table 11.50).

Table 11.50 - Cancer of the Prostate
Metastatic Spread depending on histology type
Data from Saitoh et al. 1984

	N	% without
Adenocarcinoma	1,340	27.7%
Poorly Differentiated	98	7.1 (')
Transitional - Squamous	32	9.4 (')
Unspecified	415	33.3
Total	1,885	27.5

(') P<0.01

Reporting on autopsy data on 1,885 japanese prostate cancer patients, Saitoh et al. noted that 27.5% were without metastases, indicating as above that a large number of patients die with a still locally confined or cured cancer (table 11.51). Further data are:

Patients with only one metastasis : 4.6%
with two organ metastases 7.4%
with three or more 60.5%

The distribution obtained more or less corresponds to the data of Lamothe et al, butsuch data, as always, depend on the diligence of the pathologist.

In patients without lung involvement, there was significantly less bone and liver involvement as well as for adrenal and kidney metastases, but they are not absent. In patients with only single organ involvement, one-third had bladder invasion only, though these are not true metastases. Solitary bone metastases (33% of the patients with only one site) are much more frequent than lung only (5% of the patients with only one site).

No particular site preference is noted depending on the histology type, except somewhat more lymph nodes in poorly differentiated cancers, as well as more tumor mass within the pelvic cavity.

Table 11.51 - Cancer of the Prostate
Metastatic Spread - Autopsy data (N=1367)
Modified from Saitoh et al.

Pelvic		SupraDiaphragmatic	
Lymph node	68.0%	Bone	66.8%
Urinary Bladder	39.2	Lung	49.1
Seminal Vesicle	3.9	Thyroid	2.1
		Pleura	8.3
Abdominal		Heart	3.0
Liver	36.6	Skin	2.6
Adrenals	17.3	Brain	2.1
Kidneys	10.6		
Ureter	8.4		
Pancreas	5.0		
Intestine	4.4		
Spleen	4.2		
Peritoneum	9.9		
Rectum	9.4		

A thorough autopsy study on prostatic cancers in Basel has recently been published by Bubendorf et al. based on 1,589 patients (1967-1955). The cancer was unsuspected at autopsy in 46.7%. They provided interesting data as the correlation of the metastases with stage, grade and tumor size (table 11.52). The observed distant metastases are in table 11.53. The data on involvement of lymph node stations will be quoted in the following section. They also made several correlations between lymph node involvement and bone metastases.

Distant metastases were present in 65.8% of all patients with known metastases and only in 9.4% of those where they were not suspected, the latter being detected mostly in microscopic size.

The authors observed a close association between the presence of involved para-aortic nodes and bone metastases: when the pelvic nodes were involved, 64% had dis-tant metastases whereas the figure was 89% when the para-aortic were involved.

Overall, 35% of the patients had distant metastases, of which 90% in the bone. There was a significant association between involvement of para-aortic nodes and bone metastases (57.5%), while it was 38.6% when the nodes were negative.

Table 11.52 - Cancer of the Prostate
Pathology of the Tumor and Incidence of Metastases
Data of Bubendorf et al.2000

Stage	(N=1393)	Grade	(N=1029)	Size	(N=891)
pT2	4.2%	1	7.5%	<2 cm	4.2%
pT3	41.1	2	33.4	2-4 cm	23.7
pT4	80.3	3	60.7	4-6 cm	61.3

Table 11.53 - Cancer of the Prostate
Distant Metastases at Autopsy (N=556)
Data of Bubendorf et al.2000

Pelvi-Abdominal		SupraDiaphragmatic	
Ureter-Urthra	3.4%	Brain	1.6
Mesentery	1.1	Thyroid	1.6
Peritoneum	7.0	Pericardium	2.5
Kidney	3.1	Meninges	5.9
Stomach-Bowel	1.8	Lung	45.7
Pancreas	1.4	Pleura	21.0
Spleen	2.2		
Adrenal	12.8	Bone	90.1
Liver	25.0	Other	8.3

Despite the strong associations, 71 (or 19.7%) of the pT4 tumors had no detectable metastases. Of the tumors smaller than 2 cm, 7.9% had no metastases.
Simultaneous metastases to spine and other distant sites was seen in 48% of the patients. Metastases to bone only was observed in 33% and to other sites only in 19% (Bubendorf et al.).
The three pathways responsible for metastatic spread from prostate cancer are illustrated in fig. 11.11.

Lymphatic Spread

It was previously thought that the prostate had no lymphatics, as the pelvic lymph nodes escaped the imaging methods available in that period. The advent of lymphography and later of CT revolutionized the oncology of prostate cancer, but also the staging and treatment.

Much work has been devoted to the prostatic lymphatics. The prostate has a rich lymphatic system around the acini. Rudimentary lymph nodes are positioned along the acini and the efferent ducts. The larger vessels arising from the lymphatic network spread in a radial direction and form a periprostatic lymphatic network. Several groups of lymphatic trunks have been identified (Balogh et al.):

1. one at the posterior face of the prostate, passing to the bladder and lymph nodes along the iliac artery;
2. from the posterior face of the prostate to the median hypogastric nodes;
3. from the posterior face of the prostate along both sides of the rectum to sacral lymph nodes;
4. those following the urethra and internal pubic arteries from the anterior part of the prostate.

Recently much attention has been given to spread along the perineural and perivascular spaces, the former being the probable cause of neuralgic pains in the region.

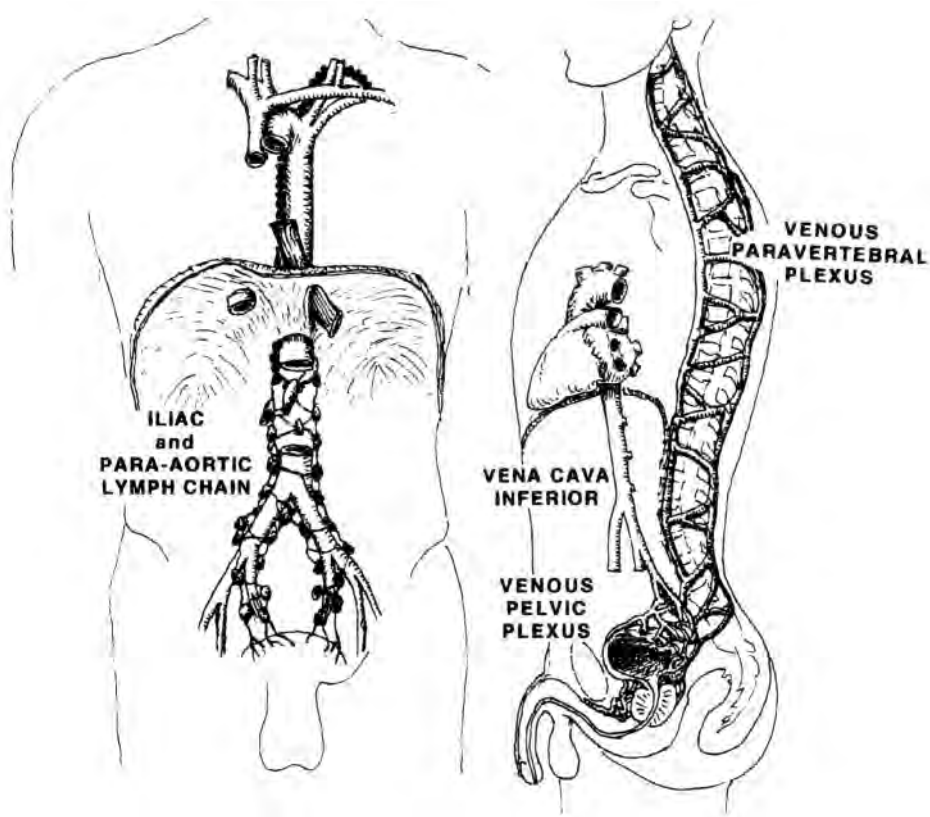

Fig.11.11 - The three different pathways of metastatases from a prostatic carcinoma. Left the lymphatic pathways, right the venous pathway, both the systemic along the vena cava inferior and the para-vertebral plexus of Batson

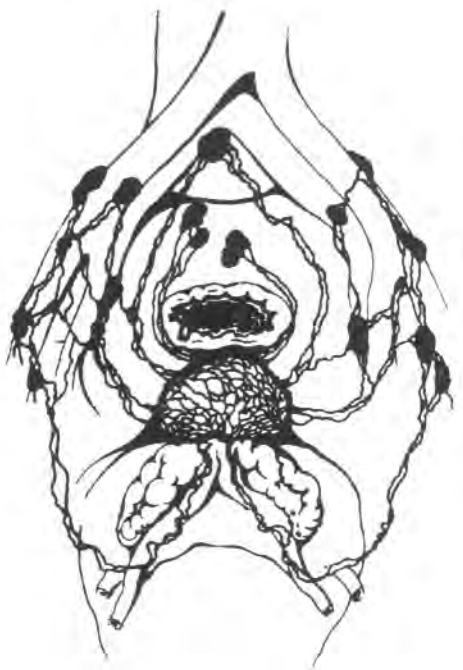

Fig.11.12 - Lymphatic spread from the prostate gland.

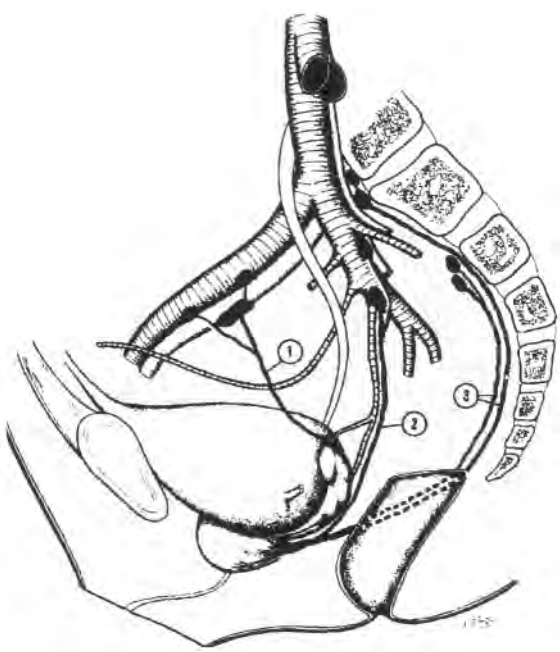

Fig.11.13 - The lymphatic drainage of the prostate: 1. external iliac chain; 2: hypogastric chain; 3. posterior chain (from Prando et al., with permission)

From the prostate, the lymph drains along three chains; the external iliac, the hypogastric and the posterior chain. The external iliac nodes, including the obturator node in its medial group are visualized by pedal lymphangiography. They comprise the majority of lymph nodes most frequently involved in prostate cancer. The nodes of the obturator fossa and the presacral nodes are not visualized with this technique. Almost in every case the lymphography opacifies the hypogastric nodes below the origin of the internal iliac artery.

Some authors have tried to obtain lymphography by patent-blue injection directly into the prostate. Smith et al. could visualize most of the routes, but were able to note also some direct filling of pre-aortic nodes.
Precise anatomic data on the involvement of prostatic lymph nodes are scarce compared with what has been reported for gallbladder, stomach and other tumors. In the hundreds of reports, only global positivity is mentioned.

Table 11. 54 - Cancer the ProstateGland
TNM-rules for lymphatic spread

Definitions:
Regional lymph nodes are the pelvic nodes below the bifurcation of the common iliac arteries
Juxtaregional lymph nodes are the inguinal, the common iliac nodes and the para-aortic nodes

N0: No evidence of regional lymph node involvement
N1: Involvement of a single homolateral regional lymph node;
N2: Involvement of a contralateral or bilateral or multiple regional lymph node;
N3: Involvement of fixed regional lymph node(s). Fixed mass on the pelvic wall with free space between it and the tumor:
N4: Evidence of involvement of juxtaregional nodes

The TNM-UICC rules have led to some anatomic simplification in the data reporting, as it has its significance for treatment policy and prognosis.

We found more precise anatomical data in the reports of Schubert et al. (table 11.55).

Table 11.55 - Cancer of the Prostate
Involvement of anatomic lymph nodes stations
Data of Schubert et al. N=62 with positive nodes(‘), compared with data of Balogh et al. (N=39)(°)

Lymph station	Right	Left	Balogh
Visceral	15.6%	--	--
Obturatorius (N1)	5.8	7.7	55.2%
Iliaca Interna (N1)	9.7	13.2	50.0
Iliaca Externa (N1)	10.5	8.8	44.7
Iliaca Communis (N2)	13.2	9.1	--
Pelvic	--	--	13.0
Abdominal	--	--	86.8
Other	--	--	13.9

(‘) Data of 102 patients with lymphadenectomy
(°) advanced cases

The obturator and the hypogastric nodes in the pelvis are probably the only nodes involved in 30% of patients with nodal metastases (Levine et al.).
CT readily visualizes those nodes that are not shown on lymphography, which indicates the superiority of CT in staging lymph nodes. However, CT has its

limitation, as small sized nodes are not found and it can not distinguish malignant from benign enlarged nodes.

Autoptic data were published by Arnheim in 1948 on 176 patients dying from prostate cancer. He particularly examined the lymph node stations (table 11.56).

Table 11.56 - Cancer of the Prostate
Lymph Node stations Involved
Autopsy data in 176 patients (Arnheim)

Para-Aortic	49%	Hepatic	2%
Iliac	34%	Gastric	2%
Inguinal	15%	Tracheobronchial	27%
Pancreatic	13%	Mediastinal	7%
Mesenteric	14%	Supraclavicular	2%

In a large autopsy study of 753 patients, Saitoh et al. were able to identify two different patterns of lymphatic spread. The first group had pelvic and para-aortic nodes involved, while the other group had only para-aortic nodes involved. Each group had a somewhat different pattern of distant metastases.

Total 753 patients: Only one site	206
More than one	547
With lymph node metastases:	63%
Only lymph node involvement :	23 patients (11%)
Had no lymph metastases	37%

Pelvic lymph nodes are at autopsy not more frequent than para-aortic nodes even in the cases with only lymph node metastases.

Table 11.57 - Cancer of the Prostate
Distribution of Lymphatic Metastases
Autopsy Data in 476 patients, Saitoh et al.

	Only LyNo N=23	All N=476	
Pelvis	43%	29%	
Inguinal	13	17	
Paraaorta	78	55	
Mesentery	4	10	
Liver hilus	4	41	p<0.01
Pancreas	0	9	
Mediastinum	0	5	
Lung hilus	4	41	
Axilla	4	4	
Neck	26	23	

Table 11.58 - Cancer of the Prostate
Involvement of Lymph Node Stations (N=471)
Data of Bubendorf et al.2000

Pelvic	57%	Inguinal	18%
Para-Aortic	80%	Mediastinal	40
Peri-Pancreatic	8	Cervical	6
Peri-gastric	6	Periclavicular	5
Mesenteric	5	Others	8

Comparing the patients with pelvic and para-aortic involvement with those with only para-aortic, the authors found less frequent bladder and rectum involvement and fewer liver and lung metastases in the first group. The more extensive pelvic involvement concurred with a higher frequency of hydronephrosis.

Non-Regional Lymph node Metastases

Reviewing CT observations in 508 prostatic cancer patients, inguinal involvement was detected in 7, mediastinal in 9, retroperitoneal in 18 (massive in 5), in the neck in 3 and even one in the axilla (Long et al.). Some mesenteric metastases were also detected (2) and invasion of the psoas in one.

In a series of 47 patients with cancer of the prostate with soft tissue or non-regional lymphatic metastases at diagnosis, Saeter et al. found 35 patients with non-regional lymphatic spread (table 11.59). Half of them had supraclavicular node involvement. Unfortunately the total number of patients staged was not given.

Table 11.59 - Cancer of the Prostate
Non regional lymphatic metastases (N=49)
Data of Saeter et al.

Supraclavicular	in 24 patients
Mediastinal	6
Para-Aortic	17
Inguinal	8

A not uncommon presentation is a cervical or supraclavicular metastatic adenopathy either at presentation or during follow-up.

Several patients have been reported, where this was the first sign of the prostatic cancer. According to Jones et al., theymaybe asumed to represent 11% of all patients with cervical nodes and 20% of those on the left. The situation is frequently overlooked (See Chapter 7).

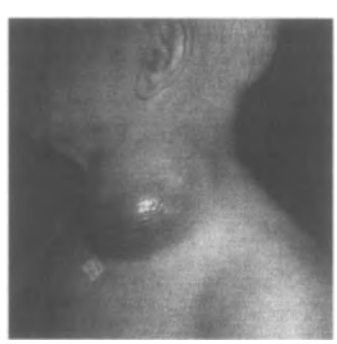

Fig.11.14 - Patient presenting with a large supraclavicular node, at FNAC an adenocarcinoma. Further exploration disclosed a prostate primary (author's collection).

Reporting on 'unusual' metastases from prostatic cancer, Tell et al. mention two cases presenting with an abdominal mass due to massive retroperitoneal lymph node involvement during follow-up and one (M58) presenting with a left supraclavicular and axillary mass as first symptom of metastasized prostatic

cancer.
Mediastinal involvement is not very well documented. Lindell et al. found it in only 12 patients out of 75 patients (16%) with an intrathoracic metastatic disease in a series of 1,435 patients.
A 75-year old patient presented with Superior Vena Cava Syndrome that had been in progress for 3 years. CT showed several mediastinal masses. Biopsy of a supra-clavicular node disclosed a prostatic cancer (Montalban et al.).

Reviewing 26 patients with metastatic prostatic cancer and supra-diaphragmatic lymph nodes, Cho et al. found all lymph nodes at the left side in all patients: 15 supraclavicular, 8 cervical, two axillary and one mediastinal. Nineteen of the patients presented with enlarged nodes alone or with prostatic symptoms. In 5 patients with prostatic cancer presenting with metastases first, the clinical sign was a supraclavicular node.

Distant Metastases

The most frequent distant metastases from prostatic carcinoma are located in the bone, the lungs and the liver. Compared with those in the bone, the pathology of the lung and liver metastases has almost not been addressed in the literature as far as distribution within the organs, number and sizes is concerned. The literature only addresses its prognosis and treatment.

Thoracal Metastases

Under this heading, we have grouped pulmonary parenchymal metastases, including the lymphangitis carcinomatosa (LC), and the mediastinal and pleural metastases as reported for prostatic carcinoma.
Reviewing 141 charts of men with prostatic cancer, Varkarakis et al. found 30 or 21.2% with lung metastases during follow-up. In the 35 patients coming to autopsy, 26 or 74.2% were demonstrated to have pulmonary metastases, of whom 23 had centrally located metastases found at radiology. In the other 106 patients without autopsy, chest roentgenograms detected metastases in only 7%. This was prior to the advent of CT.
The radiographical pattern of pulmonary lesions in 48 of 1290 patients (4%) in the series of Fabozzi et al. was as follows:

- Lymphangitic 27 (57.4%)
- Solitary nodule 11 (23%)
- Pleural effusion 3
- Mediastinal adenopathy 3
- Combined 3

In a review of 198 patients with prostatic carcinoma, chest x-ray abnormality was found in 70 patients (35.4%), but only in 48 patients, was it an oncological pathology (table 11.60).

Table 11.60 - Cancer of the Prostate
Abnormality at Chest X-ray in 48 patients
Data of Apple et al. 1985

Pleural effusion	27 or 56.2%(')
Reticular opacities	15 or 31.2%
Reticulonodular	6 or 12.5%
Nodules	14 or 29.1%
Adenopathy	9 or 18.7%

(') of the patients with radiologic abnormality, 31 patients had more than one abnormality.

This gives an insight into the pattern of thoracal metastases from prostatic cancer and are the five recognized patterns. Lymphangitis iscertainly a commonly reported situation, while relatively large solitary lung metastases are also frequently mentioned. A large series of 24 cases with LC taken from 192 files of prostatic cancer patients was reported by Karstens et al. In about half of the patients, the diagnosis was missed at first evaluation. Cytology of bronchoalveolar lavage disclosed metastatic cells from an unknown prostatic cancer. It is not clear from their report if the diagnosis was obtained from bronchial or alveolar washing. At radiology, LC was suspected (Verstraete et al.).
One case presenting first as LC has been reported by Heffner et al. in a M64.

There is a discrepancy between the rate of pleural involvement as found in autopsy series and clinical case-reports. At autopsy, the involvement was between 5 and 10% in the above mentioned series. Rapoport et al. have reported on two patients with cytology-proven malignant effusion. The case reported by Scheidemantel et al. is quoted as the first in the literature (1972) and Cassidy et al. have reported on a

Table 11.61 - Cancer of the Prostate - Patterns of Pulmonary Involvement
Modified from Carella et al.

Type	Incidence	Chest-X-ray	Clinical Presenntation
Microscopic nodules	At autopsy 25-50%	Normal	Asymptomatic
Lymphagitic carcinomatosa	Uncommon	Normal or less common fine interstitial densities	Progressive severe dyspnea, subacute cor pulmonale
Endobronchial lesions	Few cases reported	Hilar adenopathy (less commonly atelectasis, infiltrates or normal	Cough, hemoptysis, sometimes dyspnea, wheezing or asymptomatic
Diffuse tumor micremboli	Seven cases reported (all diagnosed at autopsy)	Normal	Acute dyspnea

patient (M67) presenting with dyspnea due to a massive right side pleural effusion. Cytology disclosed adenocarcinoma cells and further clinical examination disclosed a large prostatic malignancy confirmed at histology.
Reporting on one patient, Lee et al. found four patients with prostatic carcinoma who had been reported with endobronchial metastases, one as a type 1 presentation. This patient (M58) was reported by Scoggins et al. The first tentative diagnosis was a bronchial cancer. A new difficulty arose when a renal carcinoma was found, but at the insistance of the pathologist, a prostatic cancer was disclosed.

Pulmonary tumor emboli have been reported with fast progressive symptoms in a few patients, one with an undiagnosed prostatic cancer (Keeping et al.) and one 2 years after the diagnosis of a metastasized prostatic cancer (Carella et al.). Tumor emboli were found in the capillaries, arterioles and small arteries diffused throughout all lung segments (table 11.61).

Pleural metastatic effusion as presenting sign of an unknown prostatic cancer have been reported by Carrascosa et al. and Druwé et al..

Bone metastases

Occurring at autopsy in 70 to 80% of cases, bone metastases constitute the main clinical problem during the evolution of prostate cancer patients. The distribution of the metastases according to anatomic site has been reported in a few reports only (table 11.62).
It is well known that the lumbar spine is the most frequently involved site, corresponding with the tumor cell spread along the lower vertebral plexus. Some authors have dismissed this (Dodds et al.)..

Table 11.62 - Cancer of the Prostate
Distribution of Bone Metastases (N= 1367)
Autopsy Data of Saitoh et al.

Site	Whole group N=1367	Bone Only N=73
Skull	2.0 %	6.8 %
Cervical Spine	0.4	1.4
Thoracic Spine	5.0	15.5
Lumbar Spine	14.7	31.5
Spine, unspecified	13.9	26.0
Sternum	9.2	13.7
Ribs	11.4	23.3
Scapula	0.4	1.4
Ilium	5.1	12.3
Pubis	2.6	2.7
Ischium	0.4	1.4
Sacrum	1.5	4.1
Pelvis, unspecified	2.9	--
Femur	5.0	12.3
Arm	0.9	--

The high incidence of lumbar and thoracal spine metastases also brings a high risk of spinal cord compression. Figures of 7 to 14 % have been reported for prostatic cancer. The proportional rate according to level of involvementhas been found to be between 5 and 14% in the cervical spine, 46 to 68% in the thoracic spine and 18 to 48% in the lumbar spine (Osborn et al.). In a quarter of the patients, however, multiple levels were concerned (Smith et al.).
From 611 patients with prostatic cancer, 41 or 6.7%, presented or later developed spinal cord compression. The incidence was 4 times higher in poorly differentiated than in well-differentiated (12% vs 3%). Similar data have been reported by Rosenthal et al.

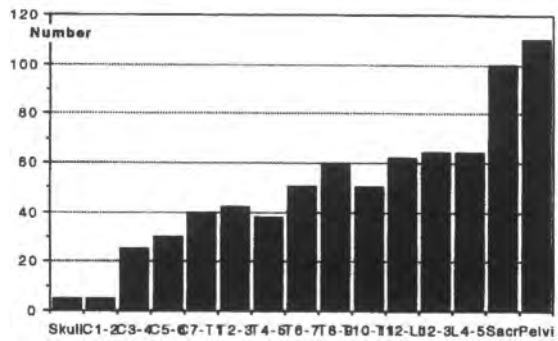

Fig.11.15 - Distribution of bony metastases on bone scintigram in 55 patients (drawn from data of Cummin et al.)

In half of the patients, the thoracic and in one third the lumbar spine was involved. The interval between diagnosis of bone metastases and cord compression ranged from 0 to 57 months, with a median of 15.5 months. In six patients the prostate cancer was found after the presentation of a spinal compression. Well differentiated cancers had a significantly longer interval. In all the 41 patients except one, the lesions were extradural (Kuban et al.).
A peculiar case was recently reported by Petit et al. in a man of 68 treated 3 years earlier. He developed asingle metastasis in the posterior arc of D6 with paraparesis. At surgery, a posterior epidural mass was resected.

In their study of bone scintigrams of 55 prostate cancer patients with bone metastases, Cummin et al. obtained a similar site distribution, but quite a lot more in the pelvis and sacrum. Figure 11.15 clearly shows the preponderance of bone metastases in the lower body half. This can also be interpreted as a gradual 'filling' of the venous plexus of Batson towards the vertebral column.

Table 11.63 - Cancer of the Prostate
Anatomical Distribution of Bone Metastases (N=71)
Data of Morgan et al.

Skull	63%	Pelvis	89%
Spine	93	Femur	49%
Ribs-Sternum	83	Distal Leg	4%
Shoulder	32	Distal Arm	1%
Humerus	34		

Data on the anatomical distribution of metastases from prostatic carcinoma are rare. We found the data of Morgan et al. quite representative (table 11.63).
Several case reports have appeared highlighting particular bone sites, outside the commonly occurring, as in the foot and ankle, the skull base with cranial nerve symptomatology in the presentation and others.
Not uncommon, even as first sign or first recurrence is the numb chin syndrome, due to bone osteolysis within the mandible.
The case reported by DeBoom et al. is a very particular one is A M68 presented with pain at the tempo-ro-mandibular joint. After many negative 'tests', a lobulated mass was finally disclosed at CT. A surgical biopsy disclosed a metastasis from a prostatic cancer, which had already metastasized widely but asymptomatically.

Fig. 11.16 - A patient with a prostatic cancer, presenting with a hypertrophic metastasis in the clavicula, two years after first treatment (Authors' collection)

The large majority of bone metastases in prostate cancer are of the osteoblastic type. Some authors have suggested that the number of osteolytic lesions increase with progressive evolution. A rare instance of skeletal metastases is the hypertrophic form (fig. 11.16), where 'new bone' is added to form a pseudosarcomatous mass (Roblot et al.).

Correlated with bone metastases are the metastases found in the bone marrow. They are, in fact, the precursors of the bone metastases.
Micrometastases were found in the bone marrow in 29 of 55 patients after surgery. Of the patients with extraprostatic disease, 65% had micrometastases and of the patient with localized cancers only 20%. The further outcome of these patients was however not reported (Wood et al.).
Bone marrow aspirate was obtained in 287 patients before prostatectomy and 24.2% were CK-18 positive. The authors could not correlate it with lymph node metastases, or other pathological features and concluded that the presence of epithelial cells in the bone marrowshould be considered an independent parameter with a still uncertainsignificance (Weckerman et al.).

Liver Metastases

Although a frequent metastatic site, we have not found any report specifically addressing the liver metastases as far as pathology and site distribution is concerned. The incidence is, however, much lower than for other pelvi-abdominal cancers.
A M75 presented with significant hepatomegaly nine years after prostatectomy. Imaging showed several cystic liver lesions, whereof FNAC confirmed the metastatic nature (Demarquay et al.).

Brain Metastases

Metastases in the brain have been studied well and several reports have addressed this topic.
It should be first stressed that neurological symptoms in this age group must be discerned from the more common neurologic deficits occuring at that age. Of 19 prostatic cancer patients with neurological symptoms, only 4 had central oncological problems and 9 with medullary problems due to spinal compression or radiculopathy. In 6, metabolic or treatment-related problems were present (Campbell et al.). On the other hand, as we will see, some cases have actually been revealed by cerebral neurologic deficits.

Reviewing data from autopsies in 339 patients, only 14 or 4% had intracranial metastases, but they concerned only 3 intracerebral metastases, 3 in the pituitary and 12 with dural involvement (Taylor et al.).

Reviewing the literature up to 1976, Catane found an incidence of brain metastases of between 2 to 4.4% at autopsies in about 1,000 cases.
A new review of the literature up to 1986 still found a low incidence of about 1% in autopsy series and even less (0.2%) in clinical series (Lynes et al.). Of the 57 reported cases, 16 or 25% were cerebral parenchymal, 5 or 8% cerebellar and 39 or 67% were meningeal carcinomatosis.
If the diagnosis is made clinically, the mean interval time is on the average 60 months or 5 years but there are always several other metastatic sites involved (Lynes et al.).
From the data reported on 8 patients by Chung et al., it would seem that in half of the patients the metastases are single, but data on site within the hemisphere are not cited.

Leptomeningeal carcinomatosis as such were rarely addressed in the literature. It has the tendency to remain clinically silent until significant growth has occurred, enough to cause irritation or compression of surrounding structures or increase intra-cranial pressure.
Although Lynes et al. mentioned that three quarters of the intracranial metastases in their study were leptomeningeal, very few authors have addressed this specifically. We found two case reports (Matsui et al. and Rubins et al.), both in patients with several other

metastases, but where the LC was the main clinical problem.
Sutton et al. have reported on two patients presenting with brain metastasis, one parietal and one cerebellar, as first sign of an unknown prostatic cancer. They found three other 'revealing' cases reported. Complex seizures and recent orbital pain, diplopia and peri-orbital swelling were found at CT to be due to a large-ring-enhancing lesion in the left anterior temporal lobe adjacent to a hyperostotic sphenoid wing. Surgery and pathology revealed a metastatic prostatic cancer (Bland et al.).

A large series of 38 patients, reported by McCutcheon et al. encompassed 24 adenocarcinomas, 10 small cell and 4 transitional cell carcinoma. Overall, there were 93 metastases detected, with 31% in the frontal lobe, 16% in the temporal, 14% in the occipital and 11% in the parietal lobe. An additional 25% were in the cerebellum, one case in the pons and 1 in the hypothalamus. A single metastasis occurred in 31%. Overall, 21 patients or 55% had one or more metastasis in the supratentorial, 7 or 18% in the infratentorial and 10 or 26% in both compartments.
Worth mentioning - and probably neglected in other series- is the fact that 16 of these patients had developed a second primary, which was responsible for their brain metastases.

One patient presenting with acute headache was first diagnosed as having an intraventricular hemorrhage but subsequently a bleeding metastasis from a known prostatic carcinoma (Smith et al.). A triple fossa metastasis extending over the orbital, middle and temporal fossae was reported in a patient of 57, presenting with eye proptosis, diplopia and decreased visual acuity (Kwee et al.).
A man presented with a CPA symptomatology, confirmed at CT as a small tumor. Surgical resection revealed prostatic histology, confirmed at further examination (Flickinger et al.). A similar case had been reported previously by Maiuri et al.
We also found three reports on brain stem metastasis: One patient presenting with an inferior red nucleus syndrome (Benedikt's syndrome) due to a single intramesencephalic metastasis from a prostatic cancer (Loseke et al.) and an enhancing mass on CT at the left pons and left cerebral peduncle as single site of recurrence (Gupta et al.). A solitary metastasis in the brain stem was found in a M55 presenting with a facial nerve palsy two years after prostatectomy (Salvati et al.).

A study of 17,182 brains at autopsy over a period of 19 years allowed the retrieval of 872 metastatic cases of which 21 (2.4%) concerned a prostatic cancer (Demierre et al.). They were able to identify three types of cranial involvement in prostatic cancer: bone and dura mater in 5 cases, brain only in 9 and bone, dura mater and brain in 7 cases. According to Cheng et al., the subdural space is rarely involved in prostatic cancer.
A rare presentation with chronic subdural hematoma has been reported in a few cases of prostatic carcinoma (Bucci et al. two cases; Chang et al. and Vonofrakos et al., both one case). All occurred several years after first treatment. A large right temporoparietal intracerebral hematoma combined with a small acute subdural hematoma was found at CT to be the presentation of what at histology was a metastasis of a well differentiated adenocarcinoma of the prostate, confirmed by the urologist (Barolat-Romana et al.). The authors could retrieve 4 other cases in the literature before1982.

A rare case of metastases within the ventricular system was reported in a patient (M53) presenting with mental confusion 8 months after transurethral resection (Lee et al.). CT had shown multiple metastases in the basal cisternes and the ventricular system.

Head and Neck Metastases

Bone metastases from prostatic cancer in the orofacial region are quite common, especially in the bony orbit and the mandible. Metastases in the base of the skull can reveal themselves by wat of cranial nerve palsy but have to be differentiated from intracranial metastases.

In most of the patients presenting with H&N metastases, these metastases are the symptoms of a widespread metastatic process as, either the cases presenting first or those during the follow-up, represent 'top of the iceberg'. Apart from some bony metastases, very few 'soft-tissue' metastases have been reported, most as revealing metastases. Such cases arouse more interest than similar metastases in patients known to have widespread metastases in the terminal phases.
Particular sites of which several cases have been reported, are the sphenoid sinus for the bony region and the parotid salivary gland.

The case reported by Tatcher et al. presented with a 'parotid' swelling which turned out to be an impressive osteolytic (hypertrophic) metastasis in the condyle of the mandible. The reported cases of H&N metastases from prostatic cancer are in table 11.64.

Ophthalmic Metastases

Bony metastases in the orbital walls can have a repercussion on the motility of the eyeball by involvement of the muscles or by compression of the cranial oculomotor nerves, but also on the vision by compression of the optical nerve. Quite a number of prostatic cancers present first as cranial nerve palsies (Rao).

Pure intra-orbital metastases have been described and are much more frequent than uveal (choroidal) metastases, while the reverse is the case with other primaries. According to the number of reference, there

are 3 times more orbital metastases for prostatic cancer than choroidal.

Table 11.64 - Cancer of the Prostate
Head and Neck Metastases - Literature Cases

Author Year	Pat.	Site	Interval
Bony - Sinuses			
Sorbera 1966	M67	Mandible	Type 1
Brownson 1969	M74	Frontal sinus	Type 1
Albers 1970	M68	Mandible	5 yrs
Barrs 1979	M57	Sphenoid sinus	--
Mesa 1977	M52	Mandible	Simult.
Barrs 1979	M61	Sphenoid sinus	--
McClatchey 1985	M55	Sphenoid sinus	no data
Matsumoro 1986	M79	Sphenoid sinus	--
Leduc 1986	M75	Sphenoid sinus	Type 1
Har-El 1987	M77	Maxilla	3 yrs
Tatcher 1986	M68	Condyle Mandib	Type 1
Mickel 1990	M67	Sphenoid sinus	--
Saleh 1993	M71	Nasal Cav-Maxilla	3 yrs
Mehra 1998	M79	Mandible	1 yr
Upper airways			
Quinn 1957	M83	Larynx	--
Quinn 1957	M74	Thyroid cart+Lar	--
Glanz 1978	M68	Ri.Epiglottis	Type 1
Coakley 1984	M64	Subglottic	6 mo
Hessan 1986	M70	Larynx-Thyroid	Type 1
Grignon 1990	M70	Larynx	1.5 yrs
Park 1993	M66	Thyroid cart.+Lar	Type1
Millar 1994	M85	Tonsilla	Type1
Parotid gland			
LiVolsi 1979	M77	Ri. .parotid	4 yrs
Kucan 1981	M72	parotid	--
Gruber 1989	M68	Le. parotid	Type 1
Moul 1989	M71	Le. parotid	Type 1
Hrebinka 1993	M69	Le. parotid	8 mo
Kirkali 1995	M83	Le. parotid	Type 1
Simpson 1997	M65	Le.parotid	3 yrs

Compared with other primaries, orbital metastases from prostatic cancer present at a much older age, due to the higher age of patients with this tumor. This should be borne in mind when an elderly person presents with an orbital tumor.
In 1985, Boldt et al. were able to report on 8 cases, seven being at the right side and three the first presentation of an unknown prostatic tumor. Other authors have also reported on small series since then. Three cases with revealing metastases have been reported (Aubert et al.; Khan et al.; Maschka et al.) and one case with simultaneous bilateral involvement (Green et al.). We found about 30 references on orbital metastases from prostatic cancer, totalling 40 cases.

Uveal metastases are much less frequent in prostatic cancer. Nevertheless, DePotter et al. could collect 7 cases from their own files, suggesting that it is probably underreported (table 11.65).

The patient reported by Zappia et al. had a mass lesion of the optic nerve with invasion of the choroid.

In the series reported by DePotter, there was one patient with a metastasis in the iris, a rare metastatic site.

Table 11.65 - Cancer of the Prostate
Uveal Metastases - Reported Cases

Author Year	Pat.	Site	Interval
Zappia 1972	M61	Central	Revealing
Dieckert 1982	M54	Le.Temporal	Revealing
Rigot 1989	M64	Central	Revealing
Liu 1992	M69	Le. Nasal - Infer	4yrs
Keyzur 1995	M65	Le.Sup.Tempor	4yrs
Wiegel 1998	M61	Ri.Poster.Pole	3yrs
Hill 1998	M74	Ri.Infer.Tempor.	Revealing

Urologic Metastases

The lymphatic channels common with the gonads and the other urinary and pelvic organs must explain the reflux of tumor cells towards these sites, when lymphatic channels or venous circulation becomes obstructed. This does not exclude hematogenous metastases but the distinction is impossible to make.

The most frequently involved sites are the seminal vesicles. Long regarded as a prognostic factor, it is involved in about 30% to 50% of the cases.

The other most frequently involved sites are the testicles and the epididymis, though the penis is also frequently reported as being metastatic site. Reviewing the literature in 1988, Aubert et al. found 73 cases repor-ted.
The testis should be involved in about 2% or less of the autopsies of prostate cancer patients. Of 100 testicular metastases encountered, 30% may be expected to come from the prostate.
Frequently resected as a therapeutic measure (orchidectomy), histological examination of the testis can disclose metastases in several cases. In 124 patients subjected to the procedure, Kirkali et al. found only 3 cases or 2.5%. Of 284 'therapeutic' orchidectomy specimens, metastatic carcinoma was found in 4 patients, an incidence of 1.4% (Escoffery et al.). EPrior to this, a patient subjected to hormonal orchidectomy was reported by Silverton. Metastases can also present during follow-up. Han reported on a M70 with testicular metastasis 9 years after first treatment.

Metastases in the epididymis are much rarer. Only about 15 cases should have been reported (table 11.66). Some were found at staging, other at orchidectomy.

Buchholz et al. state that between 1885 to 1994, 73 cases of penile metastases from prostatic cancer have been reported, 22% of all penile metastases reported. They occur either in advanced cases or during follow-up concomitant with other usually pelvic recurrences and metastases. They are almost always located in the corpora cavernosa and prepuce, while urethra and the

corpus spongiosum are very rarely involved (Iverson et al.). Twelve years after transurethral resection, a man (M80) presented with dysuria due to multiple urethral tumors confirmed as metastases (Tell et al.).

Table 11.66 - Cancer of the Prostate Metastases to the Epididymis Reported

Author	Pat	Side	Interval
Humphrey 1944	M63	Left	6 mo
Brotherus 1960	M55	no data	at staging
Broth 1968	M81	Left	at staging
Wilenius 1969	M59	Right	at staging
Kovi 1974	M70	Left	at staging
Puigvert 1978	M67	Left	at staging
Talbot1979	M70	Right	at staging
Addonizio 1981	M67	Right	4 yrs
Cia 1981	M73	Bilateral	1.5yrs
Sarma 1983	M59	Right	orchidec
Bahnson 1985	M66	Left	clinics
Rizk 1990	M63	Right	orchidec
Sneiders 1990	M77	no data	2 yrs
Sneiders 1990	M81	Left	2 yrs
Anastasiadis '98	M65	Right	Clinics +orchide

True bladder metastasis are rarely reported, as most are contiguous invasions. Nevertheless, bladder metastases are reported in 30% of the patients. A few cases of bladder metastases during follow-up have been reported (Buchholz et al.).

In 1978, Petit et al. reported on two cases of true ureteral metastases and found 17 other reported cases. It was bilateral in 22%. It can occur at each level, without any preference. At pathology it has either a nodular tumoral aspect or an infiltrating form. Another patient (M53) was reported by Benejam et al. According to the description, lymphatic spread towards intraluminal deposits can be suspected. Four years after transurethral resection, a M64 was found to have intra-luminal masses in the right ureter (Jung et al.).
A bilateral ureteral obstruction was found in a patient (M62) about 3 years after first diagnosis. The left ureter had extrinsic compression through periureteral lymph nodes, while the right was occluded by a bulky metastasis growing through the wall and within the lumen (Zollinger et al.).

Among other patients with prostatic cancer and urological metastases, Johansson et al. singled out two patients with metastases to the spermatic cord.

Metastases to the Skin

Cutaneous metastases have been described in a number of patients. It concerned mostly plaques of either a lymphangitic aspect over zones of the abdomen or the thigh, or multiple miliary cutaneous efflorescences in a circumscribed zone. As they are most common on the abdomen and thigh, they probably have a lymphatic origin caused by reflux due to extensive pelvic involvement.
According to Cox et al., the clinical aspect of skin metastases in prostate cancer seems to be very variable. Reviewing the literature, they found descriptions as varied as violaceous nodules, ulcerating tumors, vascular lesions, sebaceous cysts like tumors, zosteriform lesions, 'turban' tumors and erysipeloides carcinoma.
Recently, Ng et al. reported on a patient (M72) presenting with a metastatic erysipeloid cutaneous 'cellulitis' over the thigh, seven years after prostatectomy. Later, erythematous plaques developed over the abdomen, inguinal region and both thighs. The lesion was confirmed at histology as metastatic.
In another reported case involving the inguinal region, a patient (M72) presented with verrucous tan and brown-red nodules mimicking melanoma and extending to the thigh, 8 years after first treatment for the prostatic tumor (Segal et al.).

Other Metastases

Several unusual and infrequent sites have been reported.
Quinnan et al. reported on a patient (M47) presenting with cardiac tamponade. Cytology disclosed an adenocarcinoma. The diagnosis of prostate cancer was made at autopsy, where only mediastinal metastatic nodes were found.

Metastases to the breast have been reported mainly in patients receiving estrogenic treatment, but also in others. According to Kitano et al., up to 1983 there were 23 cases reported. The diagnosis can be hampered by the presence of gynecomastia.
One of the cases of 'atypical' metastases reported by Tell et al., had a breast tumor as first manifestation of metastatic prostate cancer (M70).
We are aware of three cases presenting with a pituitary metastatic mass as first sign of a prostatic cancer (table 11.67).

Table 11.67 - Cancer of the Prostate Revealing Pituitary Metastases

Couldwell 1989	M61	bifrontal headache, peripheral vision loss
Perloff 1992	M71	abrupt onset of diplopia
Losa 1997	M77	blindness, ophthalmoparesia, mental deterioration

One rare case of thymic metastases was reported in a man of 65 with a known one-year history of prostatic cancer. He presented with coughing and shortness of breath. In the right mediastinum a CT-shadow was found which at surgery was found to be a thymus involved by a metastatic tumor (Hayashi et al.).
We found two cases of metastases to the esophagus (Gore et al.; Nakamura et al.), the latter as first sign. One patient having a splenic metastasis, manifesting by flank pain (Naseem et al.) and one patient was subjected to adrenalectomy in the follow-up because of a solitary adrenal metastasis (Sakamoto et al.).
Another patient (M66) was noted with progressive

weakness and frank weight loss. CT demonstrated bilateral adrenal masses and an enlarged prostate was finally found at rectal examination with adenocarcinoma at histology. Laparotomy confirmed adrenal metastases (Navarro et al.).

Gastrointestinal tract involvement is rare. Stomachal metastases were diagnosed at endoscopy in a man (Holderman et al.). Further exploration following histology led to the discovery of a prostatic cancer. Reviewing the literature, they found a 2 to 3% involvement of the GI tract (esophagus, stomach and intestine) mentioned in literature series. Colorectal involvement has claimed to be more frequent, 2 to 13% of the cases. Dysphagia occurred in a M75 five years after diagnosis of prostatic cancer. At last, a surgical biopsy unvealed submucosal infiltration in the stomach with extension to the esophagus causing the achalazia (Eaves et al.).

Some metastases in the biliary system have been described, mostly symptomatic due to biliary obstruction. One case of a 'Klatskin' tumor metastatic at the bifurcation of the hepatic bile duct was, however, reported as first sign of a prostatic cancer in a M77 (Chen et al.).
A similar case of a M78 presenting with obstructive jaundice was reported by Cole et al. Several metastatic nodes around the common bile duct were observed at Ultrasonography and confirmed at CT at the retroperitoneal, peripancreatic, periceliac and peri-aortic sites. Rectal examination revealed a nodularly enlarged prostate. Widespread bone metastases were also detected.

Peritoneal involvement is mentioned by Saitoh et al. as occurring in 10% of the patients coming to autopsy. Almost no reports have addressed this aspect. We found a report by Wynn et al. on a M73 presenting with an omental mass nine years after first treatment. CT showed enlarged mesenterial nodes, omental cake and thickening of the sigmoid colon wall.
Two other cases have been reported of patients presenting with ascites. The patient of Disdier et al. had massive retroperitoneal nodes with positive ascites-cytology and prostate biopsy, while the diagnosis in the patient of Beigel et al. could be confirmed only on biochemical grounds
Recently, Saif et al. reported on positive cytology of ascites metastatic of an prostatic adenocarcinoma. The anatomical reason or CT findings were not discussed further.

A subcutaneous swelling in the supratrochlear region at the right elbow occurred in a M75, 4 years after diagnosis of prostatic cancer. Surgery disclosed a necrotized muscle metastasis involving the biceps, the triceps and brachialis, with extension to the flexor and extensor compartments of the forearm (Ward et al.). We are not aware of other muscular metastases reported in respect of prostate cancer.

Overall Lesson

Prostate cancer is an insiduously growing tumor, spreading first in the lymph nodes, but in quite a number along the hematogenous pathways. The main clinical presentation is extensive bone metastasis, though the relative rarity of the other metastatic sites can be misleading.
As fig. 11.17 attempts to show, prostate cancers follow a triple pathway to metastasize, the venous plexus of Batson, the lymphatic vessels and the venous circulation along the pelvic and caval veins.

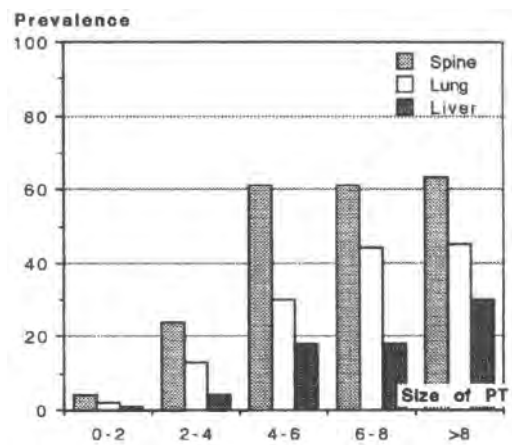

Fig.11.17 - Gradual and sequential increase in vertebral, pulmonal and hepatic metastases with size of the prostate cancer in 891 patients (autopsy data). Redrawn from Bubendorf et al.

The various different autopsy data provided by several authors may confirm the participation of the venous plexus of Batson, particularly the data of Bubendorf et al.
In the first place, an inverse relationship has been observed between the prevalence of spine and pulmonary metastases, meaning that each pathway is independent.
The smaller tumors have a higher frequency of spine involvement compared with the maximum spread to liver and lung in larger tumors, suggesting that the vertebral involvement occurs before lung and liver.
The gradual decrease of metastatic involvement from lumbar to cervical corresponds a progressive upward spread along the spinal veins of the plexus of Batson

METASTASES from CANCER of the PENIS

Cancer of the penis is a rare neoplasm. It comprises less than 1% of all malignancies in the male, at least in the Western world.

The rich vascularity, vascular as well as lymphatic, enables cancer cells to spread towards either the rich lymphatic network or to gain access the blood circulation to establish distant metastases. The latter way is, however, less common.

Lymphatic Spread

After local progression and invasion of the internal structure of the penis, cells spread to the superficial and deep inguinal network. From there, they reach the pelvic nodes; more precisely, the iliac lymph and the para-aortic nodes. In certain circumstances some reflux flow towards more caudally situated lymphatics can be observed (fig. 11.18).

The UICC-TNM classification considers only the inguinal nodes as regional nodes. Their involvement only is considered in the codification as Nl in the evidence of involvement of unilateral movable nodes, N2 the involvement in bilateral movable nodes, and N3 the presence of fixed nodes. N4 could be pelvic nodes but is not attributed.

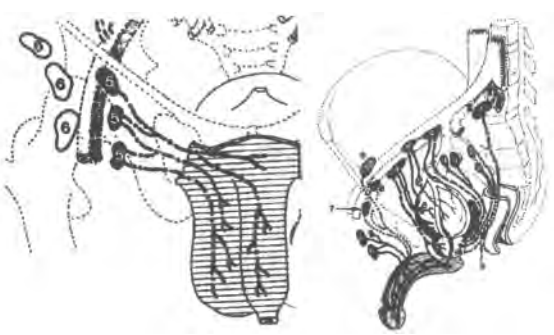

Fig.11.18 - The lymphatic drainage of the penis, towards the inguinal and pelvic nodes (from Brühl et al., with permission)

There areabout no adequate data on lymph node involvement in the literature (table 11.68).

Table 11.68 - Cancer of the Penis
Lymph node involvement (N=145)
Data of Lopez et al.

Stage'	N	N+	Stage(')	N+
T1	2	50%	N0	41%
T2	40	55	N1	65
T3	85	53	N2	51
T4	7	28	N3	83
TX	11	54	NX	50

(') clinical stage: N+ means histologic confirmation

The incidence of positive lymph nodes more or less parallels the T-factor, but many T4 patients will have no positive lymph nodes.
The same authors also examined the pelvic nodes in 35 patients with unilateral involvement. The inguinal nodes were positive in 77%, the inguinal and iliac in 20%, and in 3%, only the iliac nodes were positive.

Distant Metastases

In cancer of the penis, distant metastases are apparently rare, but not unknown. They are usually stated as occurring in 1-3%, with as most common sites liver, lungs, bone, brain and skin. Other reviews give figures of 1-10%. Lopez et al. reporting on a series of 145 patients mention a figure of 4.8%, without giving the sites. The highest rate reported is 22% in the series of Brkovic et al.
In most published series on diagnosis and treatment, some patients are said to develop distant metastases, but the site is never reported.
There are no reviewing reports on autopsy data in patients with cancer of the penis, at least not to our knowledge.
A few case-reports have appeared (table 11.69). Other reports are quoted in the reference, but inaccessible (russian or other non-western languages).
Cancer of the penis kills apparently through pelvi-abdominal spread with renal obstruction or infection.

Table 11.69- Cancer of the Penis
Case-reports of distant metastases

Mohaved 1986	M63	Ri.Ventricle	1 yr
Tharakaram 1987	M33	Skin abdomen	simult
Jacob 1995	M51	Spine D8,D11	7 mo
Lal 1999	M80	Spine D6,D11,D12	8 mo

METASTASES from URETHRAL CARCINOMA

Primary carcinoma of the urethra is relatively rare. Reviewing the literature in 1969, Waller observed that blood-borne metastases particularly in the lungs occur in one-third of cases involving the bulbomembranous urethra.
Lymph node metastases in the inguinal region and sometimes in the pelvic sites, but also in the para-aortic nodes were reported in a series of 97 patients. In 9 patients having achieved local control, distant metastases were seen mostly in the lungs (5), the other sites not being mentioned (Garden et al.).
Reviewing the records of 21 patients, Mayer et al. noted distant metastases in 6, five of them being adenocarcinomas.

Reviewing 10 patients treated for 'deep' urethra in males, Farrer et al. noted that distant metastases developed in 7 patients, but the sites are not reported.
Bone metastases were first reported in a man aged 38 by Waller. The man presented with pain and osteolyis in the distal femur, but also reported urinary problems. Since then, 14 more cases with bone metastases, seven in males and seven in female patients, have been reported, according to the review of Mirzayan et al. In five it concerned pelvic bones, one in C2 and another in the vertebrae. Site was not given in 6 patients.

One patient was reported with metastases to the glans penis (Tefilli et al.).

Reviewing the literature, Anderson et al. concluded that there was a higher incidence of distant metastases when the tumor invades the corpora cavernosa, while lymph nodes are most frequent in tumors at the distal part of the urethra. The bulbo-membraneous urethra drains directly to the obturator and iliac nodes escaping notice to the clinical examination, while the lesions at the distal urethra drain to the inguinal and then to the pelvic nodes.

METASTASES from MALIGNANT TUMORS of the TESTIS

Malignant tumors of the testis have a particular pattern of spread. Their general pathway is along the lymphatic vessels, then through the iliac, the lumbo-aortic and the posterior thoracic chains up to the supraclavicular region. A particular feature is that the involved lymph nodes can became very large, sometimes comparable to lymphoma and by their volume impact on retroperitoneal structures such as the venous plexus, the vena cava and the ureters, with an effect on renal function. The huge volume reached by mediastinal nodes can also result in a spectacular widening of the mediastinum with possible compression of the vascular structures.
Distant metastases are uncommon but not absent.

Presently, malignant testicular tumors are divided into seminoma and non-seminoma (or Non-Seminoma Germ Cell Tumors (NSGCT)). The reason for this is that each group has a specific treatment schedule. Within the latter group some differentiation can occur on an histological basis, but frequently the tumor is a mix of several types, including seminoma, embryonal cell, trophoblastic and other elements. During the last decades, aggressive chemotherapy has indeed completely renewed treatment outcome in a very favorable way to almost a complete cure in more than 80%. In the further case reports, we refer to the histology type as was reported by their authors.

Metastatic Pattern at Autopsy

There are very few studies reporting the metastatic pattern of testicular tumors.

Table 11.70 - Seminoma Testis
Metastases at Presentation (N=60)
Data of Martin et al. 1965

Lymph Node		Organs	
Inguinal	1.7%	Liver	8.3%
Para-aortic	86.7	Lungs	25.0
Mediastinal	8.3	Brain	3.3
Le. Supraclavic.	18.3	Bone	6.7

Reporting on 179 patients with testicular seminoma, Martin et al. found metastasis in 60 patients at admission, or 33.5%. The most common metastatic site was the retroperitoneum (table 11.70). These data date back to before the CT and lymphography era. Paraortic nodes were evaluated through displacement of the ureters. They undoubtedly reflected only the 'top of the iceberg'. When Calman et al. reported the status at diagnosis of 199 patients with seminoma, they found that 121 (or 61%) had no metastases at all, and were stage I patients. A positive lymphogram of the retroperitoneal space was seen in 27%, and beyond the diaphragm in 4%. In 7%, distant metastases were found.

Autopsy data have been published by Bredael et al. on 154 patients. Distant parenchymal metastases were encountered in 141 or 91%, of whom 105 had concomitant retroperitoneal lymph node metastases. Distant metastases were present only in 36 patients, or 23% (table 11.71).

Table 11.71-
Malignant Tumors of the Testis (All histologies)
Pattern of Metastases at Autopsy (N=144)
Data of Bredael et al. 1982

Abdominal		Unusual Sites	
Liver	73%	Skin	N=7
Kidney	30	Peritoneum	N=7
Adrenal	29	Thyroid	5
GI tract	27	Heart	3
Pancreas	14	Gallbladder	3
Spleen	13	Breast	3
Infer.vena Cava	11	Urin.Bladder	2
		Pericard	2
Supra-Diaphragmatic		Ureter	2
Lungs	89%	Penis	2
Pleura	17	Spinal Cord	2
Diaphragm	7	Prostate	1
Bone	30		
Brain	3		

The same authors made a distinction according to histological types for the most frequently involved organs(table 11.72). The pattern was similar everywhere.

Table 11.72 - Malignant Tumors of the Testis
Pattern of Metastases at Autopsy (N=144)
according to histology type
Data of Bredael et al. 1982

	Liver	Lung	Brain	Bone
Embryonal(')	72%	93%	20%	24%
Teratocarcinoma	80	86	20	30
Seminoma	81	75	25	56
Mixed Chriocarc	77	100	32	35

(') Embryonal N=59; Teratocarc. N=30; Seminoma N=16; Mixed choriocarc. N=30

Previously, Johnson et al. reported an autopsy series performed on 78 patients, of whom 19 pure seminoma at presentation. Histology did not reveal many differences in the site distribution, although seminoma

patients had relatively more metastases in the bone, adrenal and other abdominal organs.

The rest of the literature on metastatic testicular cancer is fragmentary.
Discussing chemotherapy in 19 advanced testicular tumors, Einhorn et al. gave the following details:

Retroperitoneal nodes and/or masses	in 11
Mediastinal and/or supraclavicular nodes	in 3
Lung metastases	in 8
Liver metastases	in 5
Bone metastases	in 2
Brain metastases	in 1

Without mentioning the number of patients treated, Baniel et al. reported on 81 patients with relapse two or more years after treatment (table 11.73). These data more or less parallel the figures reported on previous tables.

Table 11.73 - Malignant Tumors of the Testis
Site of Relapse 2 or more years after treatment (N=81)
Data of Baniel et al.1995

Nodes Retroperitoneal		53%
Mediastinal		12
Neck		10
Pelvis		7
Parenchyma	Lung	23
	Liver	9
Other		6

One general conclusion that can be reached is that the threat of lymph node invasion in the retroperitoneal space and the mediastinum, more than the parenchymal involvement. Lung involvement is, howver, more frequent than liver. The retroperitoneum serves as a cell reservoir from which further spread occurs towards lungs and liver. In addition, other distant metastases are more random and much less frequent. This may be explained by the fact that the lungs are the first parenchyma reached by tumor cells from the lymph nodes along the thoracic duct to the systemic circulation. Further metastases are already third order metastases.

Lymphatic Metastases

The testicular lymphatics (fig. 11.19) follow the testicular vessels (vena and arteria spermatica). The first lymph node is located at the lumbo-aortic level, from where it spreads further towards the mediastinum.
The most common pattern of spread from a left-sided tumor is a lymph node center at approximately the level of the left renal hilum. This node is not visualized in bipedal lymphography.
The primary lymph node group for right-sided tumors is located at a more variable level, between L1 and L3. This primary node can be seen on CT in the precaval, paracaval or inter-aorto-caval region.

Any further lymphatic spread will be to the ipsilateral and contralateral para-aortic nodes, the retro-crural region at the diaphragm and further in the mediastinum.
Teratomas metastasize in a predictable fashion. This is initially along the testicular lymphatics to the para-aortic nodes and subsequently to the mediastinum and neck or by vascular invasion with hematogenous spread.

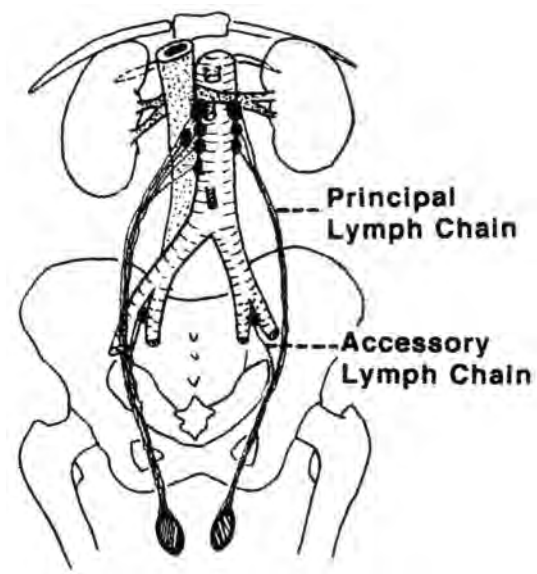

Fig.11.19 - The lymphatic drainage from the testicles

The continuous need to perform retroperitoneal lymphadenectomy in order to know more about its influence on prognosis has lead to a codification of the lymph node stations, but data on their respective involvement are rather scanty. A German multi-center study has however shed light on the problem and has allowed some conclusions to be made (Weissbach et al.).
The retroperitoneal channels converge at a cistern at the L1-L2 level, forming the thoracic duct. The duct passes the diaphragm between the descending aorta and the vena azygos. The thoracic duct remains in the posterior mediastinum, near the esophagus in the azygo-esophageal recess. It crosses the left side of the mediastinum at the level of T5, the tracheal bifurcation. It ends at the junction of the left subclavian and internal jugular vein (Wood et al.).

Seminoma spreads in a near-contiguous fashion from the abdominal nodes through the diaphragm along the thoracic duct. Reflux to the neck in the supraclavicular fossa may occur. NSGCT, on the other hand, follow a less strict pattern, the spread being much less contiguous, while nodes in the posterior mediastinum and subcarinal can occur. Neck disease can be found without mediastinal nodes being involved.

Table 11.74 - Malignant Tumors of the Testis
Codification of the Lymph Node Stations in the Retroperitoneum (Weissbach et al.)

1 Paracaval upper	6 Paracaval lower
2 Precaval upper	7 Precaval lower
3 Interaorto-caval upper	8 Interaortocaval lower
4 Pre-aortic upper	9 Pre-aortic lower
5 Para-aorticupper	10 Para-aortic lower
11 Ri Common Iliac	12 Le Common Iliac
13 Ri External Iliac	14 Le External Iliac
15 Hilar and suprahilar zone	

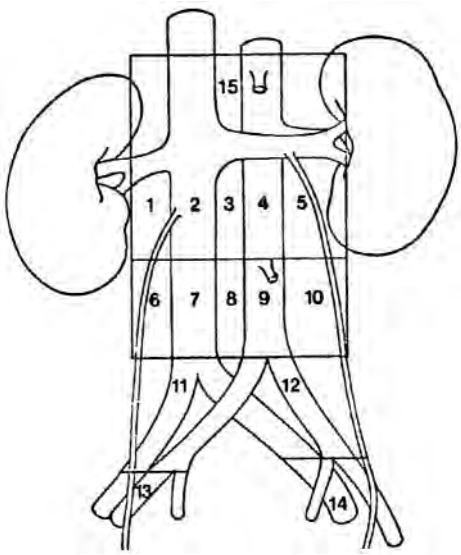

Fig.11.20 - Surgical zones of the retroperitoneum instaured to code for the topographical location of involved nodes (Weissbach et al., with permission)

Table 11.75- Malignant Tumors of the Testis
Distribution of Lymph Node Metastases (Stage II)
Data of Weissbach et al.

	Group 1 (‘)		Group 2 (“)	
	Ri(N=36)	Le(N=38)	Ri(N=30)	Le(N=23)
Zone				
1	5.6%	--	17%	--
6	14	--	20	--
2	8.4	--	23	4
7	11	2.5	37	--
3	27.5	--	33	13
8	16.5	2.5	20	--
4	5.6	10.5	10	30
9	--	--	3	13
5	--	76.5	17	74
10	--	8	--	30

(‘) solitary metastases, nodes smaller than 5.1 cm
(“) less than 6 nodes, smaller than 2 cm

Ray et al. had previously shown that there is a considerable variation in cases of right-sided tumors and only para-aortic involvement in left-sided tumors.
Weissbach et al. divided the retroperitoneal zone into a grid partitioning the surgical field in 15 zones, in order to facilitate topographic identification and reporting (fig. 11.20). The names of the surgical zones are shown in table 11.74.

We tabulated results of the pathology of the excised lymph nodes in stage II patients, excluding bulky disease (table 11.75).
The data clearly show the asymmetric involvement according to the side of the primary.
Paracaval involvement is low at this stage of disease and non-existant in left side tumors.
One can conclude that all nodes right of the aorta, from the renal hilus to the iliac bifurcation, can function as sentinel nodes. Nodes outside this area are only found when the sentinel nodes are positive.
Solitary nodes from right-sided tumors are located with decreasing frequency in upper and lower interaortocaval, lower paracaval and precaval, upper precaval and right common iliac, upper paracaval and upper pre-aortic zones.
Nodes from left-sided tumors are predominantly in the upper para-aortic zone, while the other zones are rarely or not involved, at least at stage II.
When multiple (more than 5) lymph nodes are involved (data not shown), spread is seen over the entire retroperitoneum.

Wood et al. have examined the location of residual masses after chemotherapy in 113 patients submitted to bilateral retroperitoneal dissection. The data closely parallel the dissection data described previously (table 11.76).

Table 11.76- Malignant Tumors of the Testis
Distribution of Lymph Node Metastases
Data of Wood et al. 1992

	Le (N=53)	Ri (N=60)
With residual mass	75%	65%
Tumor present	74%	70%
Site		
Paracaval	2%	8%
Precaval	2	14
Interaortocaval	5	54
Preaortic	10	10
Paraaortic	82	10

Residual masses were found in 70% of the patients and tumor were present in 72% of these masses. For the left-sided tumors, the mass was located more commonly at the para-aortic area (82%) and the interaortocaval area was the most common site for the right primaries.

In 78 autopsies Johnson et al. noted the relative infrequency of pelvic node involvement, stressing the pathways straight to the abdominal and retroperitoneal nodes. When the pelvic nodes were involved, they noted that there was retrograde extension from extensive and large retroperitoneal nodes.

A patient (M28) presented with a large mass in the

retroperitoneum, complicated with signs of acute pancreatitis. Several investigations were done without any specific diagnosis. Only at autopsy a small nodule at the left testicle was found to be a differentiated teratoma with embryonal carcinoma, like the retroperitoneal mass (Mössner et al.).

Non-Regional Lymph Node Metastases

Mediastinal disease is usually located with CT, and either para-esophageal (8R and 8L) in seminoma or subcarinal (7) in NSGCT. There is no relationship to the side of the tumor in the testis (Wood et al.).
When the mediastinal nodes are involved, neck nodes, either supraclavicular or scalene nodes, are involved in 91% of the seminomas and 65% of the NSGCT-patients.

Another factor to be considered is that, from the retroperitoneal nodes, which can outgrow to bulky masses, the tumor can spread into neighbouring spaces and organs, such as lumbar vertebrae, vena cava and the M.Ilio-psoas. They are possibly overlooked sites of metastasis in testicular tumors. This type of contiguous invasion is hardly discussed in the literature, even when bone metastases are reported.
Adressing this problem, Williams et al. have reported on six patients in whom psoas nodes were found. Five of the six patients had a left-sided tumor. Psoas nodes are somewhat more lateral than the para-aortic chains, and may either be overlooked at CT-studies or even at surgery. Prior to this report, Donohue et al. stated that the nodes at the gonadal veins and lymphatics were involved in 8-14%, stressing the importance of a more 'lateral' dissection.

Inguinal metastatic nodes are normally not involved in testicular cancers as they only drain the scrotum, the perineum, the buttock, the penis and the skin of the lower abdomen. Some exceptions to this rule are when the tumor invades the tunica vaginalis and when there are retrograd massive metastases from the retroperitoneal adenopathies (Corby et al.). Other cases with inguinal nodes have been reported, but in all cases a previous surgery had been performed for cryptorchidy or other pathologies.
We are aware of only one report concerning a large axillary node (Nielsen et al.).

Distant Metastases

The literature on distant metastases is meager. When discussed, their anatomical en pathological features are hardly described, with all attention being given to the prognostic influence and results of the efficient chemotherapy.
A number of features need to be addressed.
Compared with the other malignant tumors, several testicle primaries are found when the diagnosis of a metastasis is already made, as many patients being well aware of a testicular tumor, and keeping it hidden. Moreover testicular tumors are usually painless, contributing to the delay in consulting a physician and deferring the diagnosis of the primary.

Brain Metastases

This is an infrequent metastatic site, but the centralization of the treatment of testicular tumors has resulted in the observation that they are much more frequent than was previously thought. The brain is regarded as a 'sanctuary' for chemotherapy, but it nevertheless obtains some successes in cerebral metastases. The reporting of the cases is however disappointing as many features are not described.
Vugrin et al. reviewed the 242 patients treated at MSKCI[1] up to 1977 and found 38 patients or 15.7% with brain metastases. Data on site within the brain were not given, but the data according to histology are very interesting (Table 11.77). The highest incidence was found in patients with choriocarcinoma, while in the other histologies the frequency oscillated between 12 anfd 20%. As far as multiplicity is concerned, data are on table for the most frequent types. Cerebellar location are seen only in pure or mixed choriocarcinoma, while the majority are multiple. Single lesions are the rule in embryonal histology.

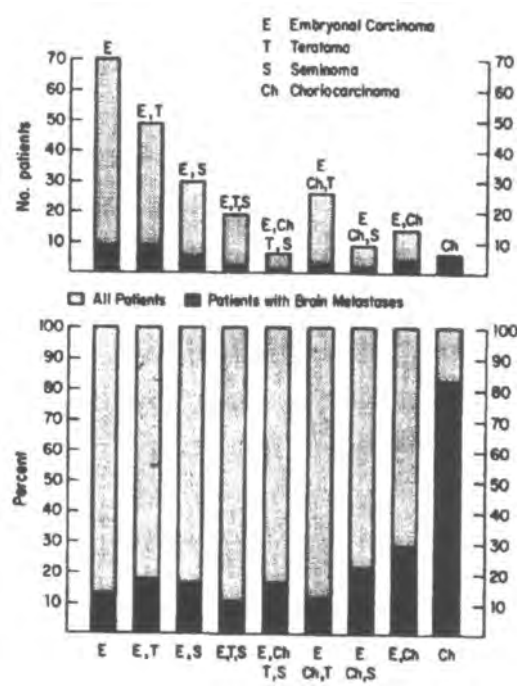

Fig.11.21 - Absolute and relative incidence of brain incidence according to histology type (From Vugrin et al., with permission)

Reporting on 22 patients treated for brain metastases, Lester et al. merely mention that about half have single brain metastases. The average length of time to

[1] MSKCC: Memorial Sloan Kettering Cancer Center, New York

diagnosis of brain metastasis from diagnosis of the metastasis was 36.5 months (range 8-110) in patients not presenting with brain metastases. The information provided by VonAhlen et al. is even more meager: they mention that the period to diagnosis of brain metastases varied from 1 and 18 months. There are no data on the site of metastases within the brain, none in the report of Bokemeyer et al. on 44 patients by Clemm et al. on 37 patients.

Table 11.77 - Malignant Tumors of the Testis
Characteristics of Brain Metastases
Modified from Vugrin et al. 1979

Histology	N	Single	Multiple	Cerebellar
Choriocarc	9	1	8	5
Embr+Chorio	2	0	2	2
Embryonal	8	6	2	0
Other	3	2	1	0

Most if not all will have simultaneously other metastatic sites elsewhere. Some case reports on brain metastases are on Table 11.78. In half of the patients, the posterior parts of the brain are involved.
A rare case of acute subdural hematoma on a metastatic seminoma occurring 2.5 years after the first treatment has been reported by Rouah et al. Three cases of hemorrhagic cerebral metastases from testicular teratoma were reported by Guest et al. In all 3 patients, the cerebral secondaries developed when other metastases were in regression, but progression was rapid.

Table 11.78 - Malignant Tumors of the Testis
Case reports on Brain Metastases

Author Yr	Test	Pat	Histol.	Site	Time
Motzer 1987	Ri	M17	Mixed	Le Front	Sim
Jelsma 1989	Ri	M17	NSGCT	Le Temp	Sim.
Delahunt '90	Ri	M38	NSGCT	Pineal	Sim
James 1992	Ri	M17	NSGCT	Le Pariet.	3 mo
James 1992	Ri	M55	Chorioca	Le Occip.	2 mo
Perry 1992	Le	M39	Semin.	Le.Occip	3 mo
Parker 1993	Le	M28	Teratoma	Ri.Frontopar	16 mo
Raina 1993	Ri	M26	Semin.	Le.Pariet	8 mo
Raina 1993	Ri	M35	Semin.	Le.Occip.	4 mo
Raina 1993	Le	M78	Semin.	Ri.Basal	8 yrs
Aydiner 1993	Le	M18	Chorioc	Ri.hemisp	Sim
Guenot 1994	Le	M24	NSGCT	Le.Occip	8 mo
Guenot 1994	--	M21	NSGCT	Ri.Occip	31 mo
Simmonds '95	Ri	M47	NSGCT	Ri.Occip.	4 mo
Yoshida 1998	Le	M43	NSGCT	Cerebell	Sim

Lung Metastases

Although mentioned as occurring frequently and in spite of the many series regularly reporting on metastasectomy, anatomical data are scarce.
Reporting on 157 patients subjected to surgery for pulmonary metastases, Liu et al. mentioned that 43 had single (solitary) lesions. Of the patients with multiple lesions, 61 had them confined to one lung and 53 had both lungs involved.

Spontaneous pneumothorax due to rupture or lysis of a pulmonary metastasis during chemotherapy has been reported (Stein et al.; Srivinas et al.).
Evidence of thoracic metastases was found in 25 of 200 patients (12.5%) with pure seminoma with chest X-rays, but in 30 with CT (15%) (Williams et al.) (table 11.79). The abnormality was not reported in 8 patients at first lecture. The most frequently involved mediastinal node is at station 7 (subcarinal) or 8, posterior mediastinum, each about 30%.

This more or less confirms that pulmonary involvement is relatively rare in seminoma, but not negligible. In non-seminomatous tumors analogous data were obtained by Lien et al. Thoracal abnormalities at chest radiology or CT were seen in 47 of 283 (16.6%) patients at presentation (table 11.80).

Table 11.79 -Seminoma of the Testis
Thoracic Abnormalities (X-ray-CT) N=30
Data of Williams et al.

Isolated Mediastinal Lymph node	12
Mediastinal node enlargement and pleural	4
Mediastinal node enlargement and pulmon meta	3
All three	2
Pulmonary metastases alone	7
Pleural Metastases (masses) only	2

Table 11.80 -Non-Seminomatous Tumors of the Testis
Thoracic Abnormalities (X-ray-CT) N=47
Data of Lien et al.

Parenchymal Metastases		39 (83%)
Any Lymph node		13 (27%
Paratracheal	4	
Hilar	1	
Subcarinal	4	
Mediastin.Post	6	
Retrocrural	6	
Supraclavicular	1	

The posterior mediastinal and retrocrural lymph nodes were the nodes most often enlarged, but also the most difficult to detect at conventional chest radiography.

In one case, three years after first diagnosis of a left seminoma, a discrete nodule was revealed at chest radiography. Surgery revealed a mass growing directly into a segmental bronchus and judged to be an endobronchial metastasis of seminoma (Varma et al.). A similar case has been reported by Cooper et al. Seven years after surgery for seminoma, the patient (M39) presented with right bilobar collapse. At bronchoscopy, the carina and right mainstem bronchus were found to be seeded with polypoid lesions, further obstructing the upper and intermediate lobe. Cytology confirmed their metastatic nature.
Recently Leleu et al. reported on a pulmonary metastasis diagnosed by bronchial biopsy in a M34. The histology was a malignant germ cell tumor, but only a burnt-out right testicular tumor was found.

Bone Metastases

Metastases in the bone are not uncommon and usually present late in the evolution.
Of 297 treated for testicular or extragonadal germinal tumors, Hitchins et al. found 11 cases, though in 7 cases the bone metastases were present at diagnosis. The predominant site was the lumbar spine (9 cases) and in the ribs and skull, each 1. Only two patients had more than one site involved.
In the 78 autopsy cases, bone metastases were detected in only 15 or 19% of the patients. More than half had involvement of the lumbar vertebrae, but metastases in the sternum, the ribs and skull were also observed each in one patient. In six patients the metastases were discovered only at autopsy (Johnson et al.).
The localisation at the lumbar spine is a very likely consequence of tumorous invasion from a retroperitoneal nodal mass. One patient even had invasion of the spinal canal with compression.
A 'routine' bone scintigraphy at diagnosis in 61 patients disclosed only 2 patients with bone metastases (Merrick) and in another study only 3 of 28 (Braga et al.). A similar study in 129 patients found none with metastases (Kotzerke et al.).
Some case reports on solitary true distant skeletal metastases are shown in table 11.81.

Table 11.81 - Malignant Tumors of the Testis
Reports on single Bone Metastases

Author Yr	Pat	Test	Histol.	Site	Time
Engelstein'80	M31	Ri	Mixed	T10 humerus	simult
Collis 1985	M53	Ri	Semin	Sternum	3 yrs
Collis 1985	M32	Le	Semin	Skull	2 yrs
Kobayashi'86	M24	Ri	Semin	Temporal	1 yr
Hermann 1986	M49	Ri	Semin	Sacrum	simult
Asthana 1988	M??	??	Semin	Os Occipit	8 mo
Dieckman'92	M25	Ri	NSGCT	Humerus	8 mo
Bosco 1994	M33	Ri	NSGCT	Pubis	Simul
Porter 1996	M43	--	Semin	Mand.Cond	1 yr (?)

Table 11.82 - Malignant Tumors of the Testis
Case reports on Head and Neck Metastases

Author Yr	Test	Pat	Histol.	Site	Time
Oro-nasal cavity					
Lainson 1975	Ri	M68	Seminoma	Mandible	3mo
Glanz 1978	--	M35	Embryon.	Epiglottis	4yrs
Fantasia 1979	Ri	M21	Teratoma	Gingiva	Simul
Nespeca 1980	--	M77	ChoriocarcGingiva		Simul
Rathmell 1993	Ri	M30	Seminoma	Ri.Tonsil	9mo
Tariq 1998	Ri	M32	Teratoma	Nas.Cav.	Simul
Ophthalmic					
Kulvin 1951	Le	M22	NSGCT	Le Choroid	2mo
Rush 1981	Ri	M28	Seminoma	Ri.Orbit	4mo
Lodato 1983	Le	M27	Embryon	Le Choroid	simul
Williamson '94	Le	M26	Chorioca	Le Choroid	simul
Bettochi 1995	Ri	M22	Chorioca	LeChoroid	simul

Head and Neck Metastases

This is a rare metastatic site. Only a few case reports have been published (table 11.82).
According to Rathmell et al. only 3 other cases of seminoma metastatic to the tonsil have been reported, of which one was a solitary metastasis. Lainson et al. state that therehad been 3 previously reported cases of metastases of a seminoma to the maxillary antrum and Fantasia found two other patients with mandibular metastasis.
Kulvin mentions four previously reported cases of choroidal metastases.
Two other cases of seminoma to the orbit were mentioned in the series of patients with orbital metastases of Font et al. and of Jensen.

Metastases to the Gastrointestinal Tract

Johnson et al. mention 4 patients with esophageal metastases in their series of 78 autopsies, or 5%.
Two types of metastases can be distinguished: those resulting from contiguous invasion of duodenum and/or stomach from a retroperitoneal node and true metastases. Some will be discovered either at CT but quite a number following an acute episode of hematemesis or hemorrhage.

Metastases in the stomach usually involve a voluminous infiltration of the wall, usually at the greater curvature. Different infiltrating lesions with central necrosis were seen at endoscopy in a patient treated for seminoma 3 years previously, when he presented with peptic complaints (Fowlie et al.).
Duodenal cases usually result from posterior invasion by huge retroperitoneal masses, which then perforate and cause profuse hemorrhagia.

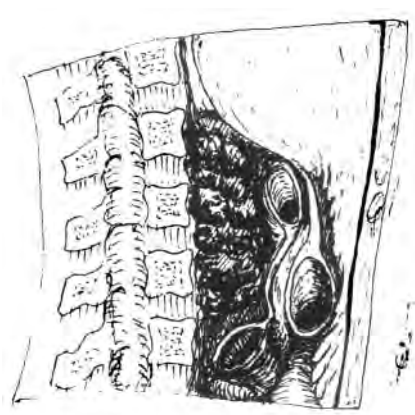

Fig.11.22 - Pending invasion of the duodenum from an invaded and enlarged retroperitoneal metastatic node.

Metastases in the jejunum will either result from tumor embolism along the mesenteric arteries and will be located at the anti-mesenteric border (Lock), or through adhesions from retroperitoneal nodes.
A rare case of a bleeding polyp in the jejunum with metastatic tumor of a choriocarcinoma from a previously treated testis tumor was reported by Meryn et

al.
The few case reports (table 11.83) spanning several decades learn that gastrointestinal metastases are uncommon, but as the reported cases have been shown to have many other widespread metastases, they are probably underreported.
Metastases to the gastrointestinal tract were found in 25 patients of a series of 487 patients with testicular germ-cell tumors (Chait et al.). Twenty of them had a histology containing choriocarcinoma-trophoblastic elements, corroborating the impression of a relatively high incidence of metastatic problems in this type.
Evidence of direct invasion was noted in 84%, but intramural tumors with submucosal extension were also seen in 20%. In general, there was no preponderant site, as stomach, esophagus, duodenum, jejunum and ileum were all concerned. There were 8 cases in the colon. Nevertheless, it seems that in the duodenum the first segment is the most frequently involved by invasion from a retroperitoneal mass.

Table 11.83 - Malignant Tumors of the Testis
Case reports on Gastrointestinal Metastases

Author Yr	Pat	Test	Histol.	Site	Time
Saliba 1966	M21	Ri	Choriocar	Stomach	
Ngan 1970	M27	Ri	Teratoma	Duoden	Sim
Nielsen 1972	M47	Le	Seminoma	Stomach	8 yrs
Lock 1975	M29	Ri	Mixed	Jejunum	Sim.
Veen 1979	M29	Ri	Seminoma	Duoden	Sim
Veen 1979	M17	Ri	Chorioca	Duoden	Sim
Veen 1979	M41	Ri	Seminoma	Duoden	Sim
Meryn 1983	M30	Le	Tera+Chorio	Jejunum	2 yr
Warhol 1983	M65	Le	Seminoma	Ileum	17yrs
Motzer 1987	M25	Ri	Embryon	Jejunum	1 yr
Cunningham	M25	Ri	Teratocarc	Duoden(°)	9 mo
idem1989(2)	M18	Ri	Teratocarc	Liver	Sim.
Plukker 1991	M32	Ri	NSGCT	Jejunum(')	Sim
Plukker 1991	M44	Le	Embryon	Duoden	Sim
Plukker 1991	M28	Ri	Seminoma	Duoden	Sim
Crookes 1992	M36	Ri	Teratoma	Duoden	10 yrs
Miller 1992	M32	Le	Seminoma	Duoden	Sim
Aydiner 1993	M18	Le	Choriocarc	Stomach	Sim
Opdam 1995	M41	Ri	NSGCT	Duoden	Sim
Weidman '96	M23	Le	NSGCT	Stomach	Sim
Hsu 1996	M31	Ri	Teratoca	Stomach	2 yrs
Nakamura 1997	M34	Ri	Embryon	Duoden	Sim
Hockenk. 1997	M34	??	Seminoma	Stomach	2 yrs
Hofflander1999	M27	Le	Mixed	Jejunum(")	Sim
Nord 2000	M24	Le	Embryon.	Duoden	Rev
Nord 2000	M45	Ri	Chorioca	Duoden	Sim

Sim: simultaneous presentation
(°) refused lymphadenectomy
(') in jejunum only choriocarcinoma
(") with intussusception

Sweetenham et al. previously had reported on 6 cases, of which three involved seminomas. Three cases were dia-gnosed with metastases at presentation.

GIT involvement was found by Johnson et al. in 25% of the 78 autopsied patients.
Most cases with gastro-intestinal metastases have many other metastatic sites, but the acuteness of the bleeding and other symptoms will disguise their presence. Moreover, almost all were self-neglected cases where a long-standing testicular tumor had been kept hidden by the patient. Only 4 cases of table had been previously treated. The majority of right testicular tumors is striking.

Metastases to the Skin

A distinguishing feature of skin metastases in testis cancers is that most are from choriocarcinomas (table 11.84). Some have been reported from non-testicular cancers and in gestational choriocarcinoma. Several were found simultaneously at diagnosis.

Table 11.84 - Malignant tumors of the Testis
Case reports on Cutaneous Metastases

Author Yr	Pat	Test	Histol.	Site	Time
Saliba 1966	M21	Ri	Choriocarc	Scapular	Aut
Price 1974	M19	Ri.	Choriocarc	Scapular	simult
Winter 1989	M27	Ri	Choriocarc	Shoulder	simult
Requena 1991	M23	Le	Choriocarc	Chest	simult
Chhieng 1995	M23	Le	Choriocarc	Scapular	simult
Shimizu 1996	M22	Le	Choriocarc	Back	9 mo
Tinkle 2001	M24	Le	Choriocarc	Face-scalp	1 mo

Cardiac Involvement

Cardiac involvement is mainly due to intracardiac extension of a tumor thrombus in patients with advanced testicular tumors (Savarese et al.). This results from invasion of vena cava from retroperitoneal nodes but can also be the clinical manifestation of the tumor at presentation (Low et al.). Reviewing the literature, Vohra et al. found 8 other reported cases, and added one of their own, presenting with syncope. Their data show that these patients are somewhat older, between 21 and 42 years, and usually have a histology of mature teratoma.
Two different types of cardiac involvement can be identified. Firstly true cardial metastases has been reported (table 11.85). Unusual is the site of metastasis in three cases, the right atrium. The long time interval is not uncommon in testis metastases.
The other type of involvement is more frequent, the intraluminal extension of vena cava tumorous thrombus up to the atrial cavity. This is a dreaded complication, as pulmonary embolism with fatal consequence is possible. Several case reports have been published (table 11.86).

Table 11.85 - Malignant tumors of the Testis
Cardiac Metastases - Literature reports

Author Yr	Pat	Test	Histol.	Site	Time
Maione 1985	M28	??	Embryon	Ri.Atrium	Type1
Esper 1987	M36	??	Embryon	Ri.Atrium	Type1
Cheek 1988	M31	Ri	Embryon	Le.atrium	Type1
Pickuth 1992	M23	Ri	Teratoma	Ri.Ventr	3 yrs
Pickuth 1992	M40	Le	Teratoma	Ri.Atrium	1 yr
ODonnell'93	M20	Ri	Teratoma	Ri.Ventr	6 yrs
Parker 1993	M28	Le	Teratoma	Le.Atrium	13 yrs

Two mechanisms may be responsible for the involvement of the inferior vena cava. Extrinsic compression by retroperitoneal masses will cause a degree of obstruction with slowing of the circulation or indirect wall irritation resulting in local thrombus formation. Tumoral invasion of the vena with formation of a real tumor thrombus is probably the most frequent mechanism in testicular tumor. The thrombus might even originate in the spermatic vein. In the previously cited autopsy study of Bredael et al., the vena cava was involved in 11%. The tumor mass may even be palpable. At CT, opacification of the vena cava intraluminal tumor zones may be very obvious.

Table 11.85 - Malignant Tumors of the Testis Involvement of the Vena Cava - Reported Cases

Author Yr	Pat	Test	Histol.	Time
Yue 1972	M17		ECC	
Resnick 1973	M32	Ri	ECC	Simult.Presentat.
Aronson 1974	M21	Le	ECC	dead at Emerg. Aut
Chiou 1984	M37		ECC	
Pillai 1986	M42	Le	Terato	pericav. mass 2 yrs
Radin 1987	M28		ECC	
Radin 1987	M21		ECC	
O'Brien 1987	M22	Ri	Sem	1week
Morgenthaler'88	M22	Le	ECC	Mass RPnode 8mc
Sharifi 1988	M29		LeTer+ECC	presenting
Jacqmin 1989	M28	Le	ECC	at staging
Stockler 1991	M17	Ri	ECC	
Stockler 1991	M44	Le	Sem	
Paule 1991	M42	??	ECC	RP mass 6 mo
Ham 1991	M35	Ri	Mixed	at surgery
Moon 1992	M25	Ri	Terato	Bulky mass 7 mo
Geffen 1992	M34	Le	Mixed	presenting
Kwok 1993	M40	Ri	Teratoma	at presentation
Savarese 1995	M25	Le	NSGCT	found at staging
Fidias 1997	M27	Ri	ECC	found at staging
Low 1999	M14	Ri	ECC	found at present.
Vohra1999	M21	Ri	NSGCT	present as syncope

A pericardial metastasis has been reported in a 32 year-old male. The symptomatology developed within weeks of surgery for an anaplastic seminoma. Sev-eral metastatic deposits were detected (White et al.).
A floating intracardiac metastasis was reported by Heik et al. in a man of 26, two years after first treatment of an embryonic cell carcinoma. He had also widespread pulmonal metastases.

Other Metastases

Unusual sites of metastases were found by CT in 20 patients (23 sites) in a series of 650 patients with testicular tumors, or less than 3% (Husband et al.). There were 6 patients with renal metastases, four in the adrenal glands, four in the inferior vena cava, three in muscles, two in the spleen, one in the stomach, one in the prostate and one in the pericardium. This demonstrates the low rate of metastases in non-lymphatic regions, which had an overall rate of invasion of 61% at any station.

Splenic metastases are rarely found ante-mortem. At autopsy, they have been observed in 10 to 15%. In a series of 11 patients where the spleen was investigated with FNA biopsy, Silverman et al. mention two cases, one (M62) with an embryonal carcinoma and one (M16) with a malignant teratoma. Both patients had also extensive disease.
Although according to Bredael et al. renal involvement is rated at autopsy at 30%, reports on renal metastases are rare. A symptomatic presentation with fever, flank pain and hematuria led to the diagnosis of a large tumor of 10 cm diameter in the upper pole of the left kidney. An enlarged right testis was found containing a mixed NSGCT (Kramer et al.).
Another report concerned a man presenting with fever and flank pain. Both kidneys were found to be diffusely enlarged and to contain seminoma at needle biopsy (Abboud et al.).

In the urologic organs, metastases have been reported in the seminal vesicle and in the prostate with resulting hematospermia.
In the upper portion of the ureter, a large polypoid intraluminal mass was noted at laparotomy. It had caused a non-functioning and hydronephrotic kidney. No other metastases were detected in this M30 operated on for a left seminoma (Johnson et al.). Recently one case of a solitary intraluminal metastasis in the left ureter was reported in a patient (M29) treated six months earlier for a left seminoma (Straub et al.). No other case with this unusual metastasis from testicular cancer has been reported.

A unusual case (M25) with only diffuse bone marrow invasion and no other metastatic sites has been described by Wassenaar et al. Ten months after surgery and radiotherapy for a seminoma, a thyroid swelling was observed in a M24 (Steinfeld et al.).

Recently, 2 patients were reported as having epidural masses, in both cases at the T7 level. In both it was the presenting symptom of a testis tumor, though it was not further described for the second patient (Arnold et al.).

Tumor Markers

Three tumor markers are well established in the management of testicular tumors: hCG, AFP and LDH. The tumor marker elevation depends strongly on the histology type or on the presence of a particular malignant population. One does need to remember that not every patient with histology of any kind of testis tumor has elevated markers. A prospective study on more than 1,000 patients disclosed marked variability and that a high proportion (>50%) are marker negative throughout the entire course of disease (Norgaard-Pedersen et al.). This means that while tumor markers are a valuable aid in the follow-up, normal values are not a sign of inactive disease (Doherty et al.).

Table 11.87 - Malignant Tumors of the Testis
Causes of Death - Autopsy Study (N=78)
Data of Johnson et al. 1976

Organ Failure		63 (80%)
Brain	30%	
Liver	17	
GIT	8	
Pulmonary	44%	
Hemorrhages		10 (13%)
Pulmonary	3	
Liver	3	
GIT	4	
Sepsis		5 (7%)

Cause of Death

Only by Johnson et al. have addressed this issue in their autopsy study on 798 patients. Death was attributed in most cases to organ failure, hemorrhage or sepsis (table 11.87). Virtually all cases of hemorrhage were due to choriocarcinoma-histology.

Metastases from Endocrine Testis tumors

Endocrine tumors of the testis are rare. Only case-reports or small series have been reported.
According to Tanaka et al. only 8 cases of metastatic large-cell Sertoli cell tumor have been reported. Metastases were observed in lung, bone liver and retroperitoneal nodes. A similar spread is observed in the few Leidig cell tumors as reported in three cases by Grem et al. and recently in a small series by Farkas et al.

Overall Lesson

We have the impression that tumors of the right testicle have the tendency to generate more metastases than those of the left. It should be remembered that the right gonadal vein joins directly the inferior caval vein. The preponderance of choriocarcinoma or trophoblastic elements is also remarkable, but trophoblastic tumors have a well-known particular aggressive invasiveness.

Testicular tumors metastasize along the lymph channels to the retroperitoneal nodes, from where they can reach the mediastinum and the lungs. More distant parenchymal metastases are rare. Their rarity constitutes one of the pitfalls in clinical oncology.
Testicular cancer will kill either by expansion of the metastatic tumors within the retroperitoneum towards its neighbourhood, by evolution of lung and liver metastases or as a result of distant metastses in strategic organs such as the brain.

METASTASES of OVARIAN CARCINOMA

Ovarian cancers can be divided in 4 types
A.Epitheliomas of the germinal layer (95%)
B.Germinal cel tumors (1%)
C.Tumors of the gondadal stroma (2%)
D.Tumors of the supporting tissue and Metastases from other tumors (2%)
The tumors of the Germinal layer are divided in
A1. Serous Cystadenocarcinoom 50%
A2.Tumors of the heterotopic Mullerian epithelium:
'cervical': Mucinous Cystadenocarcinoom: 10%
'endometr': Endometrioid cystadenocarcinoma: 10 à 20% incl. the mixed mesodermal Mullerian tumors and the endometrial stromal sarcoma
from both: clear cel carcinoma (mesonephroid tumors) 5 à 10%
(Non-epithelial cancers are discussed further)

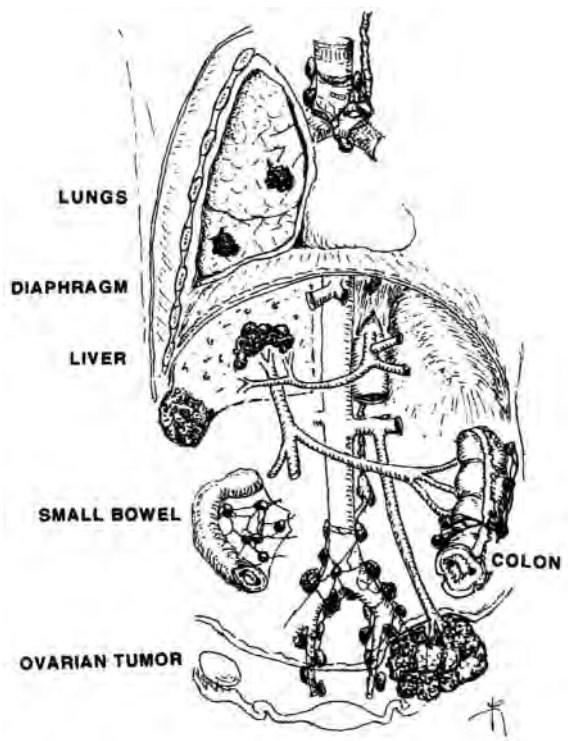

Fig.11.23 - Diagram of the various different pathways of metastasis from an ovarian carcinoma

Pathways of Metastases

Ovarian cancer is one of the most insidious cancers, both in its presentation and in pattern of spread. Several pathways are used by this cancer with both pelvic and abdominal 'characteristics' during its evolution (table 11.88, fig. 11.23). An ovarian cancer spreads mainly along two pathways, not mutually exclusive of each other: firstly intra-pelvic spread by continuous invasion and/or lymphatic towards the lymph nodes of the iliac chain, secondly by invasion

or 'perforation' of the peritoneal blade towards the peritoneal cavity, where cancer cells will colonize the peritoneal surface with secondary invasion of the intra-peritoneal organs.

Table 11.88 - Cancer of the Ovary
Pathways of Spread

1. Local (pelvic) spread by contiguous invasion
2. Invasion of the peritoneal wall and cavity with implants on the peritoneal surface
3. Invasion of the serosa and wall of the colon and small bowel, from where via the portal system to the liver
4. Lymphatic spread from the pelvis to the retroperitoneal and mediastinal nodes
5. Hematogenous via vena ovarica to vena cava

The first two pathways are responsible for about 90% of the deaths in these patients, according to autopsy studies. Death by distant metastases occur in less than 10%. The data provided by autopsy studies are illuminating in this respect.

Table 11.89 - Cancer of the Ovary
Metastases at Operation and Autopsy (N=86)
Bergman 1966

Pelvic cavity		Supra-Diaphragmatic	
Opposite ovary	71%	Mediastinal N	50%
Uterus	18	Supraclavicul N	25
Vagina	13	Axillary N	26
Vulva	(1)	Pleura Le	29
Pelvic nodes	80	Pleura Ri	37
Abdomen		Lungs	37
Peritoneum	87	Brain	(1)
Omentum	71	Pituitary	(2)
Spleen	6	Bone	14
Liver	34	Skin	8
Retroperitoneal		Thyroid	(2)
Aortic nodes	78	Heart	(1)
Kidneys	7		
Adrenals	8	P ancreas	(1)

Table 11. 90 - Cancer of the Ovary
Location of Metastases at Operation and Autopsy
Data on 52 cases, Kataoka et al. 1995

Pelvic cavity		Retroperitoneal	
Opposite ovary	--	Aortic nodes	35
Uterus	--	Kidneys	29
Vagina	--	Pancreas	73
Vulva	--	Adrenals	15
Pelvic nodes	25%	Supra-Diaphragmatic	
Abdomen		Mediastinal N	25
Peritoneum	87	Axillary N	--
Omentum	60	Supraclavicul N	8
Diaphragm	31	Pleura+Lung	32
Stomach	33	Pleura	40
Small intestine	65	Lungs	48
Large intestine	67	Pituitary	0
Spleen	52	Bone	6
Liver	73	Skin	2
		Thyroid	0
		Heart	2
		Brain	0

Autopsy Data

Several autopsy series have been published. They give a veryclear idea of the spread pattern from ovarian cancer. We re-ordened the data according to pelvic, abdominal, retroperitoneal and supradiaphragmatic sites. The pioneer article relating to the subject was of Bergman (table 11.89).

It can be noticed that most of the metastases are within the pelvic and peritoneal cavity. Data on intestinal involvement were not given but were probably very high. In spite of the high number of positive retroperitoneal nodes, the retroperitoneal organs were rarely involved.
Another series was reported by Kataoka et al. (table 11.90) and also by Dvoretsky et al. (table 11.91).
Compared with the series of Bergman, the intra-abdominal spread was better documented and shows a high incidence of GIT-involvement. The involvement of the retroperitoneal organs was also much higher and should be a frequent cause of death due by ureteral and renal involvement.

Table 11.91 - Cancer of the Ovary
Location of Metastases at Autopsy (N=117)
Data of Dvoretsky 1966

Pelvic cavity		RetroPeritoneal	
Opposite ovary	--	Aortic nodes	38
Uterus	27	Kidneys	10
Vagina	14	Pancreas	21
Vulva	1	Adrenals	15
Pelvic nodes	17	SupraDiaphragmatic	
Urinary bladder	27	Mediastinal N	29
Abdomen		Supraclavicul N	4
Peritoneum	73	Axillary N	0
Omentum	38	Pleura Le	38
Diaphragm	63	Lungs	49
Stomach	31	Pituitary	--
Small intestine	70	Brain	6
Large intestine	78	Heart	4
Spleen	51	Bone	11
Liver	70	Skin	5
		Thyroid	2

Of all the intra-abdominal organs, the serosa is much more frequently involved than the 'parenchymes'. This is interesting as it explains much of the pattern of spread of the ovarian cancer. The cells from ovarian cancers spread through the peritoneal fluid all over the various different surfaces and will eventually penetrate the serosa through the capsule into the parenchyma. We summarized the data together in table 11.92.
The conclusion is that whenever one mention fi. liver metastases, it can concern in most of the cases only a superficial (subserosal) involvement.

The hitherto mentioned autopsy series date back from long before the chemotherapy era. Ovarian cancer is now heavily treated by chemotherapy and it would be interesting to know wether the treatment has modified the metastatic pattern. It is only very recently that

Reed et al. from the NCI have adressed the question and have reported adequate data. We will first outline their overall results (table 11.93) and will discuss the influence of chemotherapy at the end of this chapter.

Table 11. 92 - Cancer of the Ovary
Type of spread on Abdominal Organs
Data of Dvoretsky

Organ	Serosa	Wall/Parenchyma
Stomach	31%	12%
Small intestine	70	52
Large intestine	78	55
Spleen	51	15
Liver	67	45
Urinary bladder	24	11

These authors were the first to make a distinction between serosal and parenchymal involvement of the liver and bowel. Remark the rather high incidence of splenic metastases.
Pseudomyxoma peritonei is rare in mucinous tumors, it was discussed in Chapter 3.

Table 11.93 - Cancer of the Ovary
Location of Metastases at Autopsy (N=93)
Data of Reed 2000

Pelvi-Abdomen		Thorax	
Vagina	12%	Esophagus	4%
Ureter	16	Diaphragm	52
Bladder	12	Lung lymphangit	12
Bowel mucosa	36	Lung parenchyme	37
Bowel serosa	86	Lymphatics	38
Liver parenchyme	59	Pericardium	16
Liver serosa	38	Pleura	51
Lymphatics	29		
Pancreas	29	Other	
Peritineum	53	Bone	15%
Spleen	44	Brain	4
Adrenal	16	Skin	5
Gallbladder	14	Thyroid	4
Kidney	4		

Lymphatic Spread

Lymph drains from the ovaries along two peduncles, one of which accompanies the ovarian vessels. The first leads to the lymph nodes at the renal hilus and para-aortic lymph nodes. On the right, it communicates with the latero-caval and inter-cavo-aortic nodes at the level of L1-L2. On the left it communicates with the pre-aortic and latero-aortic nodes. The other peduncle drains the lymph at each side of the pelvis or the lateral iliac lymph nodes.

The mediastinum can be reached by two pathways. First the lymphatic pathway from the retroperitoneal nodes and secondly from the peritoneal cavity through the diaphragm stomata. The diaphragm has a rich subperitoneal lymphatic network, allowing cells to pass through its structure to the pleural surface.
Significant spread occurs along the retrosternal lymphatics to the anterior mediastinal nodes, from its anterior part (see chapter 1). The middle part of the diaphragm will drain to the para-esophageal nodes and the thoracic duct. In the posterior region of the diaphragm, the lymph will drain to the nodes at the aortic and esophageal hiatus. They communicate with the trun-cus celiacus and upper retroperitoneal nodes (Bettendorf).
Lymphatic metastatic spread has also been observed in the inguinal nodes, the axillary nodes, the anterior supra-diaphragmatic nodes and in the supraclavicular fossa (table 11.94).

Table11.94 - Cancer of the Ovary
Lymph node Stations possibly involved

Pelvic and their subgroups
Retroperitoneal (Para-aortic and paracaval)
Inguinal
Anterior Supradiaphragmatic
Mediastinal
Axillary
Supraclavicular

If previously at surgery only sampling was performed, the advent of total lymphadenectomy has shed more light on the lymphatic spread of ovarian cancer. Compared with the codified lymphadenectomy set up by Japanese surgeons in respect of several digestive cancers, this has virtually not been done for pelvic cancers, as we already mentioned in the chapter concerning testicular cancer. Pioneering studies by the group of Benedetti-Panici, led to the knowledge of the incidence of lymph node involvement in ovarian cancer. Remember that the FIGO- staging system does not include anything about lymph node status.

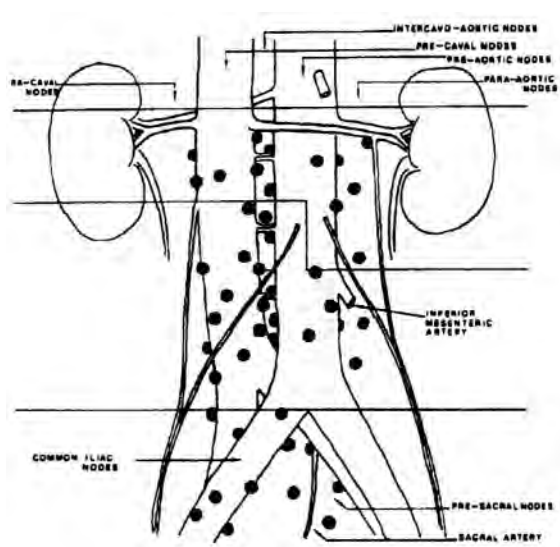

Fig.11.24 - Para-aortic lymph node stations as identified by Benedetti-Panici et al. (with permission)

As already mentioned, lymph drainage occurs along two different chains, the ovarian vein chain and the pelvic-iliac chain, both converging towards the para-

aortic. Within the two groups, different stations can be distinguished (table 11.95 & fig. 11.24). Within both groups primary stations have been identified, the 'first' stations involved, and secondary ones that become only involved later, as was demonstrated by complete lymphadenectomy.

Table 11.95 - Cancer of the Ovary
Lymph node stations as
defined by Benedetti-Panici et al.

1.Pelvic	2.Para-Aortic
Primary stations	
Common Iliac	Paracaval
External Iliac	Precaval
Obturator superfical	Pre-aortic
	Para-aortic
Secondary stations	
Obturator deep	Intercavo-aortic deep
Prresacral	Intercavo-aortic superf.
Parametrial	Retro-aortic
Internal iliac	

Data in respect of 81 patients has allowed several interesting conclusions. In 35 patients, positive nodes were observed, with a frequency largely depending on the stage of disease (table 11.96).

Table 11.96 - Cancer of the Ovary
Positive Patients at Lymphadenectomy
Data of Benedetti-Panici et al.

	N	Positive	Percent
Stage I	35	5/35	14%
Stage II	2	0/2	--
Stage III	44	30/44	68%

Of all patients, there was solitary involvement in 10 patients at the aortic area and in 11 at the pelvic area. Positive lymph nodes only at the pre- as well as para-aortic site was present in 5 and only at the pre-as well as para-caval site, also in 5 patients, or resp. in (5/35) 14% of the 'positive patients'.
In the pelvic area, the common iliac only was involved in 4, the external iliac only in 5 and only the obturator in 2 patients. If stage is considered the results obtained clearly show the 'progressive' involvement of the different sites, particularly clearly in stage III (table 11.97, fig. 11.25).

Table 11.97 - Cancer of the Ovary
Involvement of sites according to Stage
Data of Benedetti-Panici et al.

Stage I	Aortic site	2/35 =	5.7% of all patients
	Pelvic site	3/35 =	8.7%
Stage III	Aortic site	6/44 =	13.6%
	Pelvic site	5/44 =	11.3%
	Both sites	19/44 =	43.1%
in secondary stations			
	Intercavo-aortic	12/25	48%
	Retro-caval	3/25	12%
	Retro-aortic	4/25	16%
	Internal Iliac	1/24	4%
	Pre-sacral	2/24	8%

It would seem that at all stages, virtually the same number of para-aortic nodes are involved as the pelvic ones. The data allow the conclusion that at least in stage III, several lymph node stations should be submitted to dissection in order to obtain an adequate debulking. We think that the FIGO staging system should be amended according to the TNM principles.

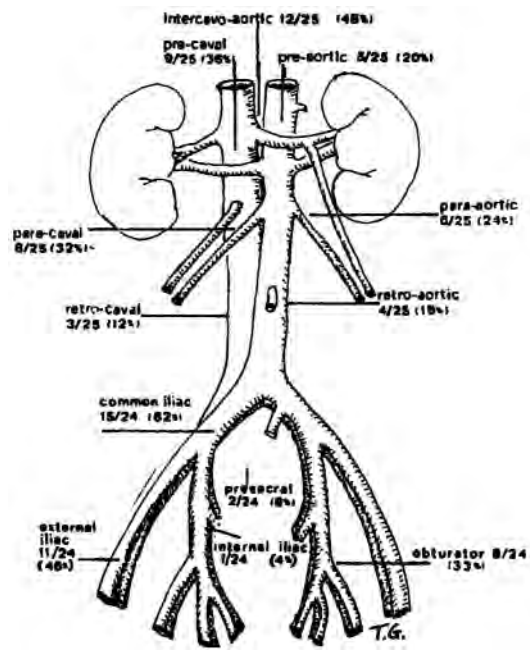

Fig.11.25 - Data obtained at lymphadenectomy in ovarian cancer Stage III by Benedetti-Pacini et al. (modified)

In spite of these data, most authors still group all nodes and label the patients as positive or negative, without further distinction. They all pay more attention to the impact on prognosis, though a more detailed review of the results would give more information about the spread and biology of ovarian cancer.

As far back as 1978, Piver et al. stressed the necessity of lymph node studies at the para-aortic level. Reviewing the limited data available at that time, Tsumura et al. found involvement at stage I-II was known at a 10% level. They did a lymphatic dissection, with a diligence usual in Japanese studies in 158 patients, of whom 115 could be fully evaluated. The overall incidence of lymph node metastasis was 25%, increasing obviously with stage: 5.9%, 23.1%,59.3% and 85.7% in respectively stages I, II, III and IV. Further data are in table 11.98.

According to these data, the pelvic route is less important than the para-aortic route. As well as this, the presence of peritoneal metastases strongly correlates with the incidence of para-aortic nodes (data not shown). It can at least be concluded that in all stages both routes will play an important role and simultaneously, and staging procedures in stage I

patient should not be limited to a pelvic dissection.
The same authors have also provided overall data on the involvement of the various different lymph stations (table 11.99).

Table 11.98 - Cancer of the Ovary
Data obtained at Lymph Node dissection (N=115)
Data of Tsumura et al.

	N	All N	Pelvic	ParaAortic
Stage I	68	5.9%	0	5.9
Stage II	13	23.1	7.7	23.1
Stage III	27	59.3	33.3	55.6
Stage IV	7	85.7	42.9	71.4
All	115	25.2	11.3	23.5

Table 11.99 - Cancer of the Ovary
Data obtained at Lymph Node dissection (N=115)
Data of Tsumura et al.

Station	
ParaAortic node above IMA(')	19/115 - 16.5%
ParaAortic node below IMA	18/115 - 15.6
Common iliac node	10/115 - 8.6
External iliac node	9/115
Internal iliac node	4/115
Obturator node	7/115
Medial deep inguinal	0
Lateral deep inguinal	8/115
Parametrial node	1/107
Sacral node	2/108

(') Inferior Mesenteric Artery

Non-Regional Lymph Node Metastases

Inguinal nodes involvement are not uncommon in advanced stages. The cells may travel along the round ligament ending behind the inguinal canal. On the other hand, there have been reports of its involvement as first sign of ovarian cancer and one as a solitary recurrence (table 11.100). In the classical sur-vey of Zaren et al., ovarian cancer was the primary in 5%.

Table 11.100 - Cancer of the Ovary
Non-Regional Lymph Node - Case Reports

Author	Pat	Histology	Interval
Inguinal			
McGonigle 1992	F59	endometrioid	Revealing
Kehoe 1993	F66	adenocarcinoma	33mo ante
Scholtz 1999	F43	ser.cystad.	solitary
Axillary			
Duda 1991	F54	pap.serous	2.5 yrs(')
Merimsky '91(2)	F53	pap.cystad.	1 yr
Höss 1997	F53 (III)	ser.papill.	15 yrs
Hockstein 1997	F78 (III)	poor diff.carc	Revealing
Bischoff 1997	F67 (III)	carcinoma	1 mo
Patel 1999	F44 (°)	carcinoma	3 yrs
Orris 1999(")	F63	pap.ser.cystad.	3 yrs
Gallo 1999(")	F59 (III)	pap.ser.cystad.	Revealing

(') inclusive 3 breast metastases
(°) prophylactic surgery for family history
(") bilateral case (2) case 2 of his report

In Chapter 7, we discussed the involvement of axillary nodes in non-breast cancer. The lymph from the anterior abdominal wall drains indeed towards the axillary region. In recent years, there have been several reports on axillary lymph node metastases in ovarian cancer, either as first sign or during its evolution (table 11.99).
Involved supraclavicular lymph nodes are found at autopsy in about 25% of the patients. They are not uncommon during evolution as extension from the retroperitoneal and mediastinal lymph nodes. Involved cervical nodes can be considered as originating from a further reflux within the lymph channels.
Reporting on a patient (F65) presenting with a nephrotic syndrome, Hoyt et al. observed a left supraclavicular mass as first sign of the ovarian cancer. The nephrotic syndrome was due to a left adnexal mass associated with periaortic nodes compressing the ureter
Positive scalene nodes have been found in about 20% of stage III-IV patients (Petru et al.). As this did not modify the staging, further studies were abandonned.
Involvement of mediastinal nodes can be observed in 10% of the patients presenting. Specific studies are not at hand.

A particular site is the anterior diaphragmatic group (para-cardial). In a series of 78 patients (Stage II, III and relapsed I), Holloway et al. detected with CT 22 patients or 28% with positive nodes at that site and in 13 more during further follow-up. This is undoubtedly a neglected site in the staging of the patients. Enlarged parasternal nodes were seen at CT in patient 2 described by Merimsky et al. when reporting on cutaneous metastases.

The recent case (F46) reported by Montero et al. is a clear metastasis within a paracardial lymph node, as can clearly be seen on the CT.
The case of sternal involvement reported by Noguchi et al. is almost certainly an invasion of the sternum by such a metastatic node.
Similar cases have been reported by Patel et al. In one, the node progressed through the intercostal space as a parasternal tumor, a situation commonly encountered in breast cancer.

Abdominal Spread (Peritoneal Cavity)

Peritoneal implantation is the main form of propagation of ovarian cancer. Tumor cells shedding from the primary tumor, lying open within the peritoneal cavity, are implanted on the peritoneal wall. Further shedding from these small implants will be carried by the peritoneal fluid. The irritation of the peritoneal endothelium will cause some overproduction of fluid eventually leading to ascites.
As discussed in chapter 3, the peritoneal fluid circulates from the lower parts of the peritoneal cavity up to the abdominal surface of the diaphragm. Most of the ascending circulation moves along the right para-colic

gutter, the main channel of communication between the infra- and supramesocolic compartments of the peritoneal cavity.

The loose cells will 'colonize' the peritoneal surface and build up a multitude of small tumors on the parietal surface as well as on the surfaces of the small and large intestine, the stomach and the liver. These will either remain within the serosal layer, or invade the wall or the parenchyma, resulting in localized intramural metastases. The secondary tumors will also disseminate further more or less in the same way as the primary tumors of these organs usually do. This is most significant for colonic metastases.

Table 11.101 - Cancer of the Ovary
Subclinical Disease at laparotomy stage I-II
Review by Piver et al. 1978

Site	N	Percent +
Diaphragma	70	15.7%
Aortic nodes	68	10.3
Omentum	36	2.7
Peritoneal cytology	87	29.8

Table 11.102- Cancer of the Ovary
I nvolvement of sites in Stage-III patients (N= 53)
Data of Kigawa et al.

Omentum	90.6%
Colon (')	26.4
Small intestine	15.1
Parietal peritoneum	22.6
Retroperitoneal lymph nodes	62.1 (")

(') not stated if serosal or wall
(") only 29 patients

Data on subclinical metastases present in stages I-II were reviewed by Piver et al., and showed that a macroscopic evaluation results in a serious understaging (Table 11.101). Remarkable is the high positivity of cytology, clearly emphasizing the submicroscopic spread present even at these low stages.
Other informative data were reported by Kigawa et al. in stage-Ill patients (table 11.102).

Peritoneal Metastases

In the previous discussions, the involvement of the peritoneum was mentioned. After having penetrated through its overlying serosa, the tumor cells from the ovarian tumor will spread and multiply within the peritoneal cavity and progressively colonize it quite extensively, paralleling the stage of disease.
In 72 patients undergoing laparotomy, peritoneal cytology was available. Ascites was present in 94%. The result of the cytology was compared with the presence of abdominal implants (table 11.103).
The high number of false-negatives can be explained by the poor mixing of peritoneal washing, and infrequent exfoliation of malignant cells. At stage III, every patient must be considered as having a positive peritoneal cytology.

Table 11.103 - Cancer of the Ovary
Results of Peritoneal Cytology- Stage III-IV (N=72)
Data of Pretorius et al.

Positive Cytology	63/79	80%
True Negative cytology	16/79	20%
False Negative observed		
in peritoneal washings		48%
in ascites		6%
at primary surgery		12%
peritoneal metast. <0.5cm		50%
peritoneal metast.>0.5cm		16%
second-look		50%
Specimen without blood		0%
Specimen bloody		25%

Several authors have pointed to calcified intraperitoneal metastases (review by Teplick et al.).
Although resection of the omentum is since long a mandatory part of the surgery for ovarian carcinoma, data on its involvement are scanty. We only found a report of Steinberg et al. who examined the omentum at histology in 109 patients. In 32 patients, it was grossly and microscopically positive, in 43 grossly and microscopically negative, but positive in 12 who were grossly negative. The situation of the 22 other patients was not described.

Liver Metastases

As already mentioned, liver metastases from ovarian cancers come through two pathways. The first is through peritoneal/serosal implants with subsequent infiltration through the serosa. The second pathway is hematogenous, and probably in a dual way. Tumor cells can come from tumoral implants within the small or large intestine along the portal circulation. Tumor cells could also come from pulmonal parenchymal metastases as 'third generation' metastases through the systemic arterial circulation.
Without giving the total number of ovarian cancers treated, Yokota et al. reported on 51 autopsy studies, of which 20 or 39% had liver metastases and on 15 cases with liver metastases diagnosed clinically. Of the latter 12 had multiple metastases and 3 a single metastasis. Of the latter 12, 11 had intra-abdominal spread, 3 retroperitoneal lymph node metastasis and 3 had pleuro-pulmonal metastases.
All of the autopsied cases had intra-abdominal tumor spread.

An autopsy review of 89 patients disclosed parenchymal liver metastases in 52 or 58% at some time during natural history (Isonishi et al.). Multiple micronodular metastases were the most frequent presentation. Thirteen or 25% of the patients with liver involvement had subscapular metastases with or without involvement of the parenchyme. According to these authors, there are proportionally more liver metastases in cases of mucinous and clear cell carcinomas.

CT studies allow a better visualization of the subserosal metastases and have shown that they can also be located at the inferior side of the diaphragm, escaping possibly resection in the debulking procedure (Lundstedt et al.; Triller et al.).
In the case described by Leifer et al., CT showed progressive lobar fatty infiltration of the liver (a common presentation of the liver at CT). Fine needle biopsy showed extensive metastatic infiltration of a serous cystadenocarcinoma of the ovary treated more than a year ago. This demonstrates that the CT aspect of focal lobar fatty infiltration can also be considered as caused by metastases.

Gastro-duodenal Metastases

Metastases to the stomach are not common, and this applies also for ovarian cancers. A number of cases are cited within reviews of stomachal cancers, but specific reports are rare. A few cases are mentioned in the seriesdealing with metastatic tumors in the stomach include a few cases (see Chapter 3).
Mibu et al. have reported on a solitary intramural metastasis at the pylorus, diagnosed after a syndrome of pyloric stenosis and confirmed at surgery as a metastasis from an endometrioid carcinoma of the ovary.

An unusual intramural gastric metastasis from a recurrent ovarian (IIIC) papillary serous cystadenocarcinoma has been reported. Five months after a negative endoscopic biopsy done because of gastric complaints, a CT dis-closed a 4 cm mass at the lesser curvature. Surgery confirmed its metastatic nature. Apparently no other metastases were found in the abdomen (Taylor et al.). A similar case was reported earlier by Majerus et al.

Two years after first curative treatment, a patient (F60) had hematemesis. An ulcer at the first portion of the duodenum was seen at endoscopy, with a specific adenocarcinoma at biopsy. At surgery, it was found to be an intra-mural metastasis (Martin et al.).

Metastases to the Small Intestine

Due to the widespread peritoneal shedding of tumor cells and the large surface of serosa exposed, implantation of tumors on this part of the GI tract is not uncommon. Inflammatory and/or desmoplastic reaction of the serosa can lead to an agglomeration of intestinal loops resulting in (sub)-obstruction syndromes. The intestine is indeed progressively involved from the external side or serosa.
Although several authors have discussed surgery and its impact on survival, few have reported interesting pathology data. Of 62 patients submitted for surgery, the small intestine was concerned in 26 cases, or 42% (Wu et al.). Ovarian tumors indeed first involve the pelvic contents, causing obstruction mainly of the large intestine in 90%, along with the lower parts of small bowel.
Other authors mention a majority of small bowel involvement. We found no specific reports about this involved site or pathology.

Metastases to the Colon

Ovarian cancer is the most frequent cause of malignant invasion of the colon. Direct invasion from the left ovary through the sigmoid mesocolon most often involved the inferior border of the sigmoid colon. Direct invasion from the right ovary usually involves the cecum and the distal ileum by extension through the small bowel mesentery of the ileum
Reviewing the files of 217 patients, Feller et al. found that colonic (sigmoidal) obstruction preceded the diagnosis of ovarian cancer in 14 patients. Ten of them were older than 60, the oldest being 92.

Metastases in the Appendix

There has been much discussion on this site. Several surgeons proceed to appendectomy during the classical debulking surgery. Data on the incidence of appendiceal metastases have, however, almost not been reported (table 11.104).

Table 11.104 - Cancer of the Ovary
Reports on Appendiceal metastases

Author		Stage			
	N	I	II	III	IV
Malfetano '87	78	0	0	69%	75%
Rose 1991	100	0	0	55	100
Bese 1996	90	0	0	21.4	50

The data clearly demonstrate that in early cases no metastases are present. Nevertheless, six cases of isolated appendiceal metastasis have been reported in stage I (review by Rose et al.).

Gynecological Metastases

Clear cut metastases wthin the uterus, vagina or vulva are difficult to diagnose, as the ovarian cancer frequently will involve these organs by contiguity.
Nevertheless, a number of metastatic situations have been described. In a review of 148 patients with FIGO III or IV, Guidozzi et al. found 7 patients with metastasis to the cervix, of which only three were considered true metastasis. In one patient, a metastatic deposit was seen in the vagina and in another in the vulva. In their series dealing with 14 tumors metastatic to the cervix, Korhonen et al. mention 6 cases from an ovarian cancer, three from a serous cystadenocarcinoma.
An unusual presentation of metastasis first to the cervix from an asymptomatic but clinically obvious ovarian cancer was reported in a F53 by MacComas et al.
Fox has reported on two patients where the ovarian cancer was first indicated by a positive screening PAP-

smear. A few cases were reported by Beyer-Boon where psammoma bodies in the smear pointed to the possibility of an ovarian primary. Likewise Fujimoto et al. treported on three cases.

Metastases to the Diaphragm

This muscular structure is covered caudally by parietal peritoneum and cranially by the parietal pleura. It will participate in the pathologies of both membranes. As the peritoneal surface of the diaphragm has a resorptive function, tumor cells will pass through towards the mediastinum or even to the pleura.
Serosal tumoral involvement has long been recognized as a sign of advanced disease. The problem in debulking procedures is that the tumors can be located at the upper side of the liver.

Data on the frequency of involvement are not frequently reported, but it can be expected that they will match the same involvement/surface unit as for most of the peritoneum. Most authors report their surgical procedures without providing pathological data.
In a limited series of 65 patients, Spinelli et al. quoted an involvement of 25% of the patients (I-III). Detailed data on serosal and muscular involvement were not found in the literature.

Metastases in the Retroperitoneal Space

Of the 51 autopsied cases in the series of Yokota et al., 31 or 61% had any metastatic process within the retroperitoneal space. Although specific details were not provided, there was involvement of the kidney, the adrenal, the pancreas, the ureter and other structures. Reports adressing specifically these metastatic sites are inexistant, however.
Metastases in these organs are only mentioned in the above-cited autopsy studies. One case was reported by Alexander et al. where 8 months after surgery, excretory urography disclosed a filling defect in the ureter, subsequently confirmed as a single metastasis.

Obviously involved para-aortic nodes with a large mass at the level of the duodenum were found to be obstructing the common bile duct in a woman of 66, presenting with jaundice. The same laparotomy disclosed a large papillary adenocarcinoma of the ovary (Rosenblatt et al.).

Supra-Diaphragmatic Metastases

Metastases to the Brain

Neurologic symptoms seems to occur frequently during the evolution of an ovarian carcinoma, so every oncologist knows or should know that not all are metastatic symptoms. From that point of view, the report of Abrey et al. is illustrative, reviewing 121 neurologic consultations in ovarian cancer patients (fig. 11.26). In only 22% a metastatic process was disclosed: 12 brain metastases, 4 leptomeningeal metastases, 4 vertebral body metastases, 4 metastases in the lumbosarcal plexus and 3 bone metastasis. Spinal cord compression was not observed in their patients.

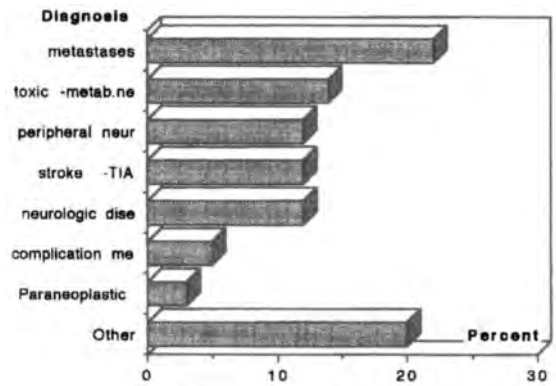

Fig.11.26 - Neurologic diagnosis in patients with ovarian carcinoma. Data from Abrey et al.

This is the only report mentioning lumbosacral problems (iliopsoas?) due to infiltration of the lumbar plexus, probably by metastatic nodes.
In the autopsy series reported above, brain metastases were hardly found, except the 6 cases by Dvoretsky et al. Since the report by Meyer et al. on 6 cases of which 2 meningeal and already labeled as a side effect of otherwise succesful chemotherapy, many reports have situated the increase in incidence due to the non-penetration of the chemotherapeutic drugs in the 'brain-sanctuary'.

The increase in the number of brain metastases could also be ascribed to a longer survival obtained through the more intense treatment of some patients (see further).
Reviewing the 47 reports in the literature, we counted 173 cases. There were 153 cerebral and 20 or 13.7% cerebellar metastasis. The 4 meningeal carcinomatosis were not counted and should be added to the eleven reports specific to meningeal carcinomatosis (table 11.105).
There were only two reports on type 1 brain metastases from an ovarian cancer (Izquierdo et al. & Matsunami et al.). The latter case however, was in fact a simultaneous presentation.
The overall interval time, as far as can be evaluated from the reports, seems to be 2years for 50% of the patients and more for the other 50%. About one third have multiple intracranial metastases. In at least 75% of the patients, disease is active elsewhere, but the lung is the other main site involved.

There is no particular intracerebral preferential site. Particular sites being one in the falx (Case 7 of Hoffman et al.) and one in the hypothalamus (Patsner et al.).

Table 11.105 - Cancer of the Ovary
Leptomeningeal Carcinomatosis
Case reports

Author	Pat	Histology	Interval
Brucher 1960	F46	carcinoma	Autopsy
Mayer 1978	F42	ser.cystaden.	14 mo
Mayer 1978	F65	poor adenocarc.	32 mo
Bakri 1983	F58	pap.ser.cystad.	78 mo
Behnam 1984	F55	ser.cystaden.	16 mo
Jackson 1984	F34	pleomorph.aden.	1 mo
Gordon 1984	F49	ser.cytstaden.	14 mo
Ross 1988	F73	adenocarcinoma	4 mo
Plaxe 1990	F29	undifferentiated	2 mo
Murthy 1991	F19	??	2 mo
Khalil 1994	F54	pap.ser.cystaden.	2 yrs
Delord 1997	F57	adenocarcinoma	2 mo
Gleyze 2000	F65	cystadenocarc	24 mo
Gleyze 2000	F38	cystadenocarc	6 mo

Reviewing the files of 4,456 patients with ovarian cancer, Larson et al. found 13 patients with brain metastases, or only 0.3%. They also mention 2 patients as having pituitary metastases. In two patients, the brain metastases were found at diagnosis of the pri-mary. The median interval in the 11 other was 24 months (range 9-120 months). In six, the metastasis was solitary in the cerebral hemisphere, in 3 it was single and in 2 there was a solitary cerebellar location. One patient had a single cerebral and a single cerebellar metastasis.
Of the eight cases reported by Kaminsky-Forrett et al., six had a single metastasis, of which 3 in the cerebellum. The two other patients had a cerebellar and a parietal metastasis. The interval ranged from 2 to 80 months, median 15 and mean 24 months.

Intramedullary or intradural metastasis has been rarely reported for ovarian cancer. Reporting on CNS metastases, Hodman described one case with metastasis in the conus medullaris. Another report of intramedullary metastasis was a case by Thomas et al. About one year after surgery and first chemotherapy, an intramedullary metastasis was seen on MRI at level C3-C7. Three months previously, she had succesful radiotherapy for multiple cerebral metastases.

A woman (F52) treated 'previously' for ovarian mucinous cystadenocarcinoma presented with low back and left leg pain. Investigations disclosed an extradural defect at L2-L3. Mediastinal nodes were also seen and two months later, a metastasis in the right parietal lobe was found (Newmark et al.).
Nguyen has reported on a patient (F46) presenting with hydrocephalus due to a cerebral and medullar metastases.

Ophthalmic Metastases

Ophthalmic metastases from ovarian cancers are excedingly rare (table 11.106). We are aware of only 5 cases to the choroid. In one, it was the presenting symptom.

Table 11.106 - Cancer of the Ovary
Metastases to the Choroid Reported

Author	Pat	St.	Histology	Interval
Hauksson 1987	F47	IV	Ser.cystadeno	8 mo
Grendys 1992	F52	IIIC	Pap.ser.	23 mo
Kushner 1997	F67	IIIC	Pap.ser.	2 yrs
Patsner 1998	F64	Iaii	Clear cell	6 yrs
Krohn 1999	F39	IV	Adenocarc	Revealing
Akahira 2000	F30	IC	Endometrioid	11 yrs

One patient (F66) was diagnosed first as having a retroorbital tumor mass, malignant at histology. Further clinical examination revealed an abdominopelvic tumor of the ovaries. The histology reported was somewhat unclear (Malviya et al.).
A young patient (F25) was reported with a metastasis in the anterior chamber of the left eye, first presenting as uveitis, about 2 years after treatment for an ovarian choriocarcinoma (Frank et al.).

Metastases to the Breast

Although considered rare, metastases to the breast are currently reported, either as first presentation or during follow-up. As discussed in Chapter 1, differential diagnosis with a primary breast cancer can be difficult. Several patients have indeed been reported as having both cancers.
A literature review in 1997 by Hennigan et al. disclosed 36 reported cases. We have listed the most important features in table 11.107. In one case, the breast metastasis preceded the ovarian (carcinoid) diagnosis by 12 months (Fishman et al.). Since this review, other cases have been reported (Peterson et al., Raptis et al., Wadhwa et al.). A few were bilateral.

Table 11.107 - Cancer of the Ovary
Metastases to the Breast
Literature review by Hennigan et al.

Histology of Ovarian Tumor	
Papill.(serous) cystadenocarcinoma	15
Serous cystadenocarcinoma	7
Other ovarian cancer	5
Other ovarian tumors (')	3
Carcinoid	1
(') granulosa (1), choriocarcinoma(1), dysgerminoma (1)	
Time of presentation:	
Found at autopsy	2 cases
No data	5
First presentation	6
Range 1 month - 10 years	
Mean: 3.3 yrs	Median: 2.5yrs

Inflammatory metastatic breast cancer has rarely been described. Only three case reports were found (Fondrinier et al.).

Pleuro-Pulmonal Metastases

The most frequent metastatic problem in the pleuropulmonal sphere is the occurrence of pleural effusion. This is most probably due to invasion of mediastinal

lymph nodes or contiguous penetration from the peritoneum through the diaphragm.
Evaluating 357 patients with ovarian cancer, Kerr et al. found some form of intrathoracic involvement in 159 patients, or 44%. At diagnosis, it was only 15%, while during evolution twice as many could be added (table 11.108).

Table 11.108 - Cancer of the Ovary
Pleuropulmonal involvement in 157 patients
Data of Kerr et al. 1985

	Principal	Overall
Pleural effusion	72.3%	77.4%
Solid parenchymal	27.6	28.3
Nodal	2.5	11.3
Pleural solid	2.5	7.5
Lymphangitic	1.8	5.7
Rib	1.8	3.8
Pericardial	1.3	1.3

Unfortunately, the status at diagnosis was not separated from the final status. Nevertheless, the presence of solid parenchymal metastases in a quarter of this group result in an overall presence of 10% of all cancer patients and of pleural effusion in nearly 30%.
Pleural effusion, even bilaterally, have been reported as first sign of an ovarian cancer (Patel et al.). In one case, according to the authors, it preceded the diagnosis by 13 years. Lethal subacute cor pulmonale due to tumor embolization revealed an ovarian cancer in a 70 year-old woman at autopsy (Veinot et al.).

Diffuse pulmonary lymphangitis is rare. We are aware of only one specific case report. Postoperative respiratory failure occurred in a woman of 45 operated upon in spite of positive pleural effusion. Bronchoscopy was normal but lavage disclosed malignant cells. A CT showed interstitial spread in both lungs (Fernandez et al.).
On the other hand, and not mentioned in the series of Kerr et al., there are several reports of endobronchial metastases (table 11.109). The primary tumor was relatively advanced in all cases. Two involved the rare site of the trachea.

Table 11.109 - Cancer of the Ovary
Case-reports on Endobronchial Metastases

Author	Patient	Histology	Interval
Seiler 1950	F47	? -Papp.Coll.	4 mo
Westerman '80	F61	IV-Papp.Cyst	6 mo (")
Merrill 1982	F45	IIB - Ser.Cyst(')	12 yrs
DeMetz 1987	F46	IB - adenocarc	8 mo
Merimsky 1990	F83	III - Pap.Adeno	<1 mo
Mateo 1992	F62	IIIB-Ser.Cyst	5 yrs
Petru 1999	F40	IIIC- Ser.Pap.	32 mo(")

(') borderline histology
(") endotracheal

One report concerns a diffuse pulmonary carcinomatous embolization. The female patient presented with an acute and rapidly fatal progressive dyspnea associated with an abdominal problem (Begin et al.). A similar case has been reported by Lambert-Jensen et al. In both cases, autopsy disclosed a widespread ovarian serous cystadenocarcinoma.

Cardiac Metastases

A few cases with cardiac involvement have been reported.
A tumor thrombus from the inferior caval vein was found at autopsy in a young woman (F53) presenting both with acute congestive heart failure and recurrent abdominal ovarian carcinoma (Basil et al.). It is apparently much less frequent than in other abdominal cancers.
A solitary metastasis at the outflow of the right ventricle was found at autopsy in a woman (F64) presenting with progressive breathlessness. It was found to be a solitary metastasis of a metastatic ovarian carcinoma detected at autopsy.
In view of the closeness of the pericard to the pleura and the mediastinum, pericardial involvement should not be uncommon. A number of case reports have been published (Lund), including two with the pericard effusion presenting as first symptom of an ovarian cancer, disclosed in one only several months later (Duflo et al., Forslund et al.).

Metastases in the Spleen

Several reports have dealt with these. In the last decades, several patients have been diagnosed with this metastatic site. In our opinion, the avenement of CT has led to a more frequent diagnosis of this unusual metastatic site.

As for liver metastases, distinction should be made between serosal and parenchymal metastases.
In the autopsy series, the parenchymal spleen is involved in about 15% of the cases. In most of cases diagnosed, it is part of widespread abdominal disease, but some solitary cases have been reported (table 11.110).
Splenectomy is not a systematic part of debulking. Of 18 patients in whom Splenectomy was performed, Nicklin et al. found 3 cases or 16% with parenchymal metastases and considered stage IV according to the FIGO rules.
Carrington et al. have reported on 5 cases of intrasplenic metastases from ovarian cancer, but the metastases were not solitary and associated with bulk disease. Recently, Gemignani et al. have reported a series of six patients subjected to Splenectomy for isolated parenchymal metastases. The median time of occurrence was 57 months or nearly 5 years (range 6-65 months).
The specific imaging characteristics at CT were examined by Spencer et al. They found that 33 of 321 patients had splenic metastases, or 10.3%. There were 10 with pure parenchymal metastases and 23 with surface or serosal metastases (table 11.111).

Table 11.110 - Cancer of the Ovary
Solitary Metastases in the Spleen at Follow-Up
Literature Data

Author	Pat	Stage	Interval
Nosanchuk 1988	F58	(II?)	2.5 yrs
Farias 1993	F49	IIIC	6.7 yrs
	F57	IIIC	2 yrs
	F59	IV	10 yrs
	F79	IIIC	1.5 yrs
Nelson 1993	F76	II	at surgery
Max 1996	F55	IC	19 mo
Balat 1996	F67	IIIC	5.5 yrs

Table 11.111 - Cancer of the Ovary
CT appearance of Splenic Metastases
Data of Spencer et al.

Type	N	Diagnosis	Follow-up
Surface	23	17	6
Parenchymal	10	5	5

Surface disease presents in a irregular scalloped shape with broad contact with the splenic surface. The length of the surface will have exceeded the depth of invasion. Parenchymal lesions have a round shape, a clear rim of normal tissue and lesion depth exceeds the length of surface involved.

Calcification was seen in 5 patients, four at the surface and one parenchymal. Attenuation values were the same for the surface and the parenchymal lesions. The mean size of the metastases was 2.3 cm.

Bone Metastases

True metastatic bone disease is rare in ovarian cancer. Reports on vertebral or pelvic metastases due to contiguous tumorous or metastatic lymphatic masses are even scanty.
An isolated invasion of the left acetabulum has been described, manifesting 4 weeks after surgery (Sansom et al.). A widespread thoraco-lumbar spine and bony pelvis involvement was found in a F57 at presentation (Dinh et al.). The same authors also reported on a F77 treated 13 years earlier, who when admitted to Emergency was found to be dying of a severe dyspnea (due to pulmonary tumor embolism??). At autopsy, several involved vertebrae were found.

Bony metastases are probably underreported. Mettler et al. obtained skeletal isotope surveys in 104 patients and found 3 positive in stage-Ill patients and one later in the follow-up of a stage-I patient. Further imaging disclosed that 3 had lytic destructive lesions in the axial skeleton and in one, some blastic lesion within the thoracic and lumbar spine.
Three cases with extradural compression due to lytic spinal metastases were reported by Hoffman et al.
In a series of 6 patients with CNS involvement, Mayer et al. mention a patient presenting with a metastasis to the ulna. Previously, one patient (F59) had been reported with a metastases in the right thumb, about 1 year after first treatment.
A patient (F43) presented with a swollen little finger. Radiology showed a complete osteolysis. Work-up disclosed several pulmonary metastases. Histology was affirmative for an asymptomatic ovarian low-differentiated carcinoma, confirmed at laparotomy (Turan et al.).

Bone marrow involvement was seen in 12 patients out of 50 at pre-treatment evaluation, or 24% (all stages). As in other studies the further evolution was not described (Cain et al.). In several cancers high positivity rates of bone marrow has been described, in spite of a very low rate of skeletal metastases observed in the further follow-up.

Other Metastases

A woman of 56 presented with a 7-day history of total vision loss in one eye. At MRI, a large sellar and suprasellar lesion was found, which at surgery revealed a poorly differentiated adenocarcinoma. Work-up disclosed a bilateral ovarian papillary cystadenocarcinoma, a histology similar to the pituitary tumor (Wu et al.).

Skin metastases have been reported (table 11.112). They are usually multi-nodular subcutaneous deposits, almost always located over the lower abdomen, most probably indicative of lymphatic reflux. Of the same order are the several umbilical metastases reported. De Marzi found this metastasis in 6 out of 85 patients or 7%. Recently, Akahira et al. reported on a women (F30) presenting 11 years after first treatment with choroid metastases and three small scalp metastases.
Reporting on three patients with cutaneous metastases almost certainly correlated with intraabdominal recurrence and related to the surgical scar, Merimsky et al. mention one as having intradermal nodules in the thorax, though no further details were given.
Muscular metastases have also been described (table 11.112). The case reported by Abulafia et al. could well have been an infiltration of the muscle by a gluteal node.

Table 11.112 - Cancer of the Ovary
Cutaneous - Muscular Metastases reported

Author	Pat	Histol.	Site	Interval
Cutaneous				
Patsner 1988	F70	Papill.	Upp.Thigh(')	2 yrs?
Merimsky 1991	F64	Carcin.	Abdomen-Umb	2 yrs
	F53	Ser.Papil	Abdomen	14 mo
	F69	Ser.Cyst	Abdomen	30 mo
Clavere 1992	F46	Papill.	Leg, Eyelid	Type 1
(') described as herpetiform				
Muscle				
Clavere 1992	F46	Papill.	Masseter (')	Type1
Abulafia 1994	F64	Papill	Gluteal	1 yr
(') this patient had also a base of tongue metastasis				

Metastasis in the esophagus was reported in a woman of 50, 16 years after first treatment. We have the impression based on the reported image that it was rather a large mediastinal (nodal?) mass displacing the esophagus (Asamura et al.).

A tumor in the left external canal and a submandibular swelling were shown at biopsy of undifferentiated adenocarcinoma to be the presenting symptoms in a F41. At peritoneoscopy, an ovarian carcinoma was found with peritoneal implants (Adams et al.).

A pregnant woman aged 28 presented with recent back pain. Examination disclosed a large ovarian mass with widespread abdominal disease, also in the vertebral marrow and in the hypothalamus. The patient soon died, and at autopsy, placental metastases were also found (Patsner et al.).

Head and neck metastases are rare (table 11.113). We are aware of only four cases, of which 1 was a type 1 presentation.

Table 11.113 - Cancer of the Ovary
Head and Neck metastases reported

Author	Pat.	Histol	Site	Interval
Freeland 1979	F54	Cystad.	Subglottis	Autopsy
Cullen 1990	F71	Anapl.	Subglottis	Autopsy
Clavere 1992	F46	Papill.	Base of tongue	Type 1
Oeken 1996	F71	Papill.Cyst	Subglottis	7.5 yrs

A 78-year-old patient presented with a lesion simulating an urethral caruncle. Biopsy showed an adenocarcinoma and further clinical examination revealed a pelvic mass. Surgery confirmed a stage II adenocarcinoma of the ovary (Hammadeh et al.).

First recurrences

This is a rarely addressed subject, butthe few studies give some insight into the further evolution, or metastases already present at the microscopic level. In a series of 17 consecutive patients treated with cytoreductive surgery and adjuvant chemotherapy, followed by a negative second-look surgery, recurrence was observed in 11 patients. The median disease-free interval for the group as a whole was 41 months. The interval to intraperitoneal recurrence was 36 months (range 20-42) and for extraperitoneal 30 months (range 23-60). Recurrence was intraperitoneal in 5, in the brain in 3 and various in the other 3 patients (Menczer et al.).

Influence of Chemotherapy

As mentioned above, it would be interesting to know what the effect of chemotherapy is on the pattern of metastases. Autopsy data date back to long before this treatment was developed. Reed et al. have very recently reported adequate data on the subject (table 11.114). The data should be compared with those in table 11.93.

Table 11.114 - Cancer of the Ovary
Location of Metastases at Autopsy (N=73)
Data of Reed et al 2000

	Chemotherapy NONE	YES
NOT MODIFIED	N=15	N=58
Liver serosa	40%	38%
Bowel serosa	93	84
Abdominal Lymphatics	60	57
Pancreas	33	28
Peritoneum	60	52
Vagina	13	12
Bone	12	16
Pleura		
MODIFIED		
Liver parenchyme	40	64
Adrenal	0	21
Bladder	0	16
Bowel mucosa	27	38
Galbladder	7	16
Kidney	0	5
Spleen	28	44
Ureter	7	19
Lung lymphangitic	0	16
Lung parenchyme	20	41
Thorac. lymphatics	20	43
Pericardium	0	21
Brain	0	5
Skin	0	7
Thyroid	0	5

Although the number of the non-treated patients is relatively low, the trend seems very indicative for several sites. The minor effect on the abdominal serosa, pointing to the fact that these metastases are already present at diagnosis should be noted. The higher number of the metastases in the treated group must be ascribed to the longer survival, allowing an opportunity for further growth of the already microscopic or later hematogenous seeding.

Table 11.115 - Cancer of the Ovary
Causes of Death in 122 patients
Data of Krafft et al. 1981

Ileus	20.5%
Peritonitis	6.6
Ureteral obstruction	3.3
Tumor toxicity	54.1
Thoracic metastases	4.9
Pulmonary embol	4.1
Treatment toxicity	3.3
Cachexia	3.3

Causes of Death

Because of the extensive involvement of intraperitoneal organs, mainly the intestine, most of the patients will die from malnutrition and toxicity from the tumoral processes involving the gastrointestinal tract.

A first overview has been reported by Krafft et al. (table 11.115). Dvoretsky et al. reported on 100 patients and described the cause of death (table 11.116).

Table 11.116 - Cancer of the Ovary
Causes of Death in 100 patients
Data of Dvoretsky et al. 1988

Disseminated carcinomatosis		48%
Intestinal obstruction	51%	
Ureteral obstruction	28%	
Infection		17
Sepsis	43%	
Pneumonia	21%	
Sepsis+penumonia	25%	
Other	11%	
Pulmonary Embolus		8
Infection and carcinomatosis		11

Overall Lesson

Epithelial ovarian cancer spreads mainly into the pelvic and abdominal cavity. Lymphonodal spread is, however, also an important part of the metastatic process, while distant metastases are relatively rare.

METASTASES from NON-EPITHELIAL OVARIAN TUMORS

The incidence of non-epithelial tumors of the ovary is much lower than for the epithelial. Most probably behave as a benign non-metastatic tumors, but malignant cases are not uncommon, with at least pelvic recurrences.
Moreover it would seem that the incidence of distant meta-stases is much lower. From a number of reports it would seem that the malignancy is marked by pelvi-abdominal and hepatic spread, as for the epithelial cancers, including some reported supraclavicular node involvement. Metastases in other organs are very rarely reported.

Malignant Struma Ovarii

The best documented histology type as far as metastases are concerned, is the malignant struma ovarii, a rare type of ovarian teratoma. Reviewing 54 cases and the relevant literature, Devaney et al. stated that fewer than two dozen cases with histological evidence of malignant thyroid tissue located in the ovary were coupled with the development of 'bona fide' metastases. The site of the metastases was, however, not discussed. A more recent review by Berghella et al. lists bone, liver, brain, lung and mediastinum as distant sites.

Pardo-Mindan et al. stated that the incidence of malignant changes in struma ovarii is probably less than 1%. Malignant cases of struma ovarii should respond to the criteria as proposed by Pando-Mindan et al.:

1. Clearly invasive signs and/or metastases
2. A thyroid morphology of follicular or papillary carcinoma
3. Evidence of thyroid tumor includes presence of calcium-oxalate crystals, thyroglobulin, T3 and T4 at [HC.
4. Ultrastructural changes similar to thyroid cancer
5. Exclusion of a thyroid primary
6. Differentiation from strumal carcinoid or serous cystadenocarcinoma

The review by Tokuda et al. in 1983 lists 17 cases, of which 6 with liver, 7 bone, 3 lung and 2 brain metastases. Of the patients with bone metastases, three were at the skull and one presented with paraplegia. Two cases with peritoneal metastases were reported by Thomas et al., but Hasleton et al. have stated that perito-neal implants do not indicate necessarily malignancy, as benign 'strumatosis', similar to other 'ovarian-like' borderline peritoneal pathologies, can be considered. This explains the long survival observed in two cases reported by Takeuchi et al.
One particular case was reported by McDougall et al. on a women (F42) who presented with a long standing and untreated spinal compression at T2. The diagnosis of a struma ovarii was made at least 3 years after the first symptoms.
Some cases have a carcinoid element at histology. Either the strumal or the carcinoid element can metastasize (Armes et al.).

Dysgerminoma

Some reports concerning distant metastases in malignant dysgerminoma (seminoma) of the ovary have appeared. However, in spite of some relatively large series, the sites of distant metastases is never discussed. Brody reviewed 60 cases in 1961 and mentioned three patients with bone, 3 with pulmonary and 6 with hepatic metastases. Metastases were observed in inguinal, mediastinal and supraclavicular nodes, except the pelvic and retroperitoneal ones.
The report of Casey et al. concerning 25 patients, mentions a few cases with mediastinal nodes.
Fichet et al. claim a case with a revealing metastasis in the thymus of an ovarian seminoma in a F40. This was probably a mediastinal germinoma.
One month after surgery for an ovarian dysgerminoma, a mass was observed in the breast and the axilla of a F16 (Kattan et al.). Fine needle cytology confirmed metastatic disease. Silverman et al. mention another case (F26) metastatic to the breast.

Granulosa Cell Tumors

Granulosa-cell tumor is the most common sex-cord stromal tumor of the ovary, approximately 2% of all ovarian cancers. The majority are locally aggressive and recur in the retroperitoneum. Distant metastases have been reported on rare occasions.
From the dedicated Emil Novak Tumor Registry,

Cronjé et al. could report on 210 patients. The incidence of the various histologic types shows significant differnces (p=0004) (table 11.117). Data on metastatic sites were not reported, however.

Table 11. 117 - Granulosa-Cell Tumors
Incidence of Metastases according to Type
Data of Cronjé et al. 1999

	N	With Meta
Granulosa- Cell Tumor	97	12.4%
Granulosa-Theca Cell	97	2.1
Theca Cell tumor	116	1.7

Table 11.118 summarizes the case reports we could find in the literature. Note the long interval between initial treatment and the appearance of metastases.

Table 11. 118 - Granulosa-Cell Tumors
Case with Metastases Reported

Author	Patient	Site of Metastasis	Interval
Beumer 1965	F61	Bilateral Lung	2 yrs
Margolin 1985	F70	Liver	20 yrs
	F68	Liver	4 yrs
	F64	Liver	6 yrs(')
Thirumala '98	F84	Liver - Bone (L1)	10 yrs
Shimizu 1999	F62	Lung (Coin)	20 yrs

(') two other patients are mentioned, but not details

Previously, Boquoi reported on 9 patients with metastases. There were metastases in the kidney (1), coccyx (1), liver (4), stomach (1), spleen (1), bone (1), intestine (7) and ureter (1).

Other Ovarian Tumors

Three other cases have been reported.
Unclear pulmonary and cardiac symptoms with signs of brain malfunction were the presenting signs in a F35 of what turned out to be a cardiac metastasis of a primary ovarian choriocarcinoma. A peculiar case of metastasis was described at the left atrium with backward extension into the pulmonary veins and stenosing mitral outflow. It most probably concerned a pulmonary metastasis with intravascular extension to the left atrium. At autopsy, widespread metastases in the spleen, intestinal tract, kidneys, pancreas, brain and multiple in both lungs were detected (Hepp et al.).
A pure brain metastasis of choriocarcinoma from a mixed germ-cell tumor of the ovary developing during adjuvant chemotherapy in a F19 was reported by Adcock et al.
An abdominal wall metastasis after surgical resection of an immature teratoma of the ovary was most probably a implantation metastasis in the surgical scar (Swartjes et al.).

Silva et al. reported a patient (F53) with obstructive jaundice 5 years after first surgery for an endometrioid adenocarcinoma of the ovary. From their description, it would seem to be a primary endometrial cancer.

METASTASES from CARCINOMA of the FALLOPIAN TUBE

Cancer of the fallopian tube is rare.

LocoRegional Spread

Tubal tumors spread first by exfoliation of the malignant cells into the lumen, which then grow and progressively obstruct the tube. The cells can then reach the uterus and ovaries by direct extension. They can mi-grate into and throughout the peritoneal cavity. Many tubal cancers obliterate the fimbriated end, preventing further peritoneal spread (Nikrui et al.). Growth through the wall towards the serosa is common.

Quite a number of cases have been reported diagnosed after demonstration of positive cervical smear and/or curettage. So Takashina et al. could report that 28/61 or 46% had abnormal smpears. There 12 were still at stage I.

Lymphatic metastases

Lymphatic spread goes to the lumboaortic nodes along the ovarian vein. The isthmus can drain along the round ligament to the inguinal nodes (fig. 11.27).
Tumors involving the proximal portion can metastasize in the lymphatics of the round ligament to the inguinal nodes. Tumors involving the fimbriated end will more frequently metastasize to the paraaortic nodes. If the broad ligament is involved, both pelvic and paraaortic nodes are at risk (Nikrui et al.).
According to Klein, all patients with stage I are free of lymph node metastases. The rate of lymph metastases increases sharply with intra-abdominal dissemination or distant secondary growth. In a report on 17 cases, DiRe et al. noted a significant increase of node metastases with intraperitoneal stage and with grading, although two patients with tumor confined to the tube had lymph node metastases.

A specific analysis of fimbrial carcinomas has shown that they are associated with an increased risk of peritoneal spread due to their location. It would seem that the prognosis is even worse than for only slightly invasive tubal carcinomas (Alvaredo-Cabrero et al.).

Non-Regional Lymph nodes

Retroperitoneal (lumbo-aortic) nodes are involved in up to 50%, depending on stage and on the diligence of the surgeon. In a small series of 15 patients, Tamini et al. found positive lymph nodes in 8 cases (53%) and spread to the para-aortic nodes was present in 5 or 33%. There was one patient with inguinal node involvement.

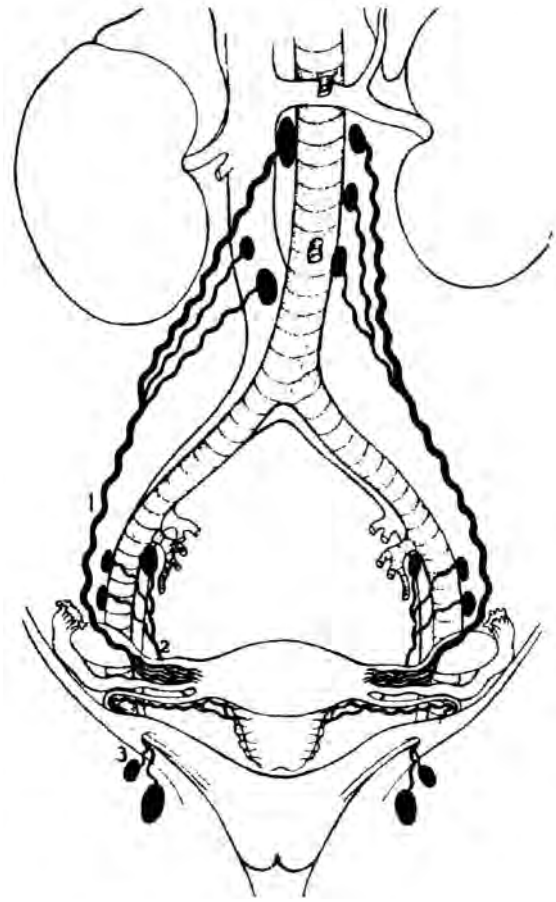

Fig.11.27 - Lymphatic drainage of the uterus and tuba and the utero-ovarian pedicle: 1: external chain up to para-aortic nodes; 2: internal iliac node; 3: round ligament and inguinal nodes. (Ackerman & Del Regato, with permission)

Compared with ovarian carcinoma, which has about the same spreading pattern, tubal carcinoma apparently produces earlier lymph node metastases in the para-aortic nodes and inguinal nodes.

Data on lymph node involvement obtained by lymph-adenectomy are available in the literature. Klein et al. operated on 21 patients. At stage I and II, no positive lymph nodes were obtained in 10 patients. At stage III and IV, there were as many positive patients with pelvic nodes as with para-aortic, resp. 9 and 7 of 11.
In 33 patients, 18 had no positive lymph nodes. Of the 15 other, 6 had only positive para-aortic nodes, 5 only positive pelvic nodes and in 3, both stations were positive. One patient had inguinal nodes.
Supraclavicular lymph node metastases are mentioned in several reports, as well as mediastinal (Semrad et al.).

Distant Metastases

In a literature survey on 232 cases of which 67 had metastases, Sedlis reported the following figures (1961):
Peritoneum 35, ovaries 22, uterus 11, intestine 4, vagina 4, 'lymph nodes' 3, liver 2, generalized 4.
Distant metastases have been described in the liver, in the mediastinal nodes, the supraclavicular nodes, skin, bone, umbilicus (Sister Mary Joseph nodule) and brain.
One case was reported presenting with metastasis in the sphenoid sinus only 2 months after first surgery. However, investigations showed metastases in the spine, the humerus and the acromion and also in the left sinus cavernosus (Merimsky et al.). Recently, several reports have appeared mentioning brain metastases (review by Cormio).

Table11.119 -Carcinoma of the Fallopian Tube Case reports on Metastases.

Author	Pat	Site of M	Interval
Couturier 1969	F70	Umbilicus	Type 1
Gale 1981	F75	Umbilicus	Simult
Young 1984	F53	Lung multiple later mult.brain	18 mo
Korhonen 1984	F52	Cervix uteri	1 mo
Korhonen 1984	F59	Cervix uteri	1 mo
Curtin1985	F44	Mandibula	2 yrs
Schneider 1986	F60	Cervix	Revealing
Silverman 1987	F54	Breast	no data
Rosen 1990	F??	Brain	6 mo
Fishman 1994	F58	Breast - pleura	3 mo
Cormio 1996	F62	Cerebellum	3 yrs
Cormio 1996	F49	Le.hemisphere	28 mo
Cormio 1996	F57	Le.hemisphere(')	2 yrs
Dubecq 1997	F68	Spleen (isolated)	6 yrs
Kouame 1998	F59	Spleen	8 yrs

(') multiple sites

One case was revealed by metastases in the cervix uteri (Schneider). Fox has reported on a F79, whose positive PAP-smear indicated an adenocarcinoma. At surgery a tubal cancer was discovered. Curtin et al. described a patient with a jaw metastasis two years after surgery. This was the first clinical sign of widespread metastasis.

Metastasis in the breast from a papillary adenocarcinoma was reported in a case, though the description pointed more in the direction of a primary peritoneal carcinoma (Fishman et al.).
Two cases with symptomatic and solitary splenic metastases have recently been reported (Kouame et al.). One case presented first with metastases at the umbilicus (Galle et al.).

Table 11.119 gives an overview of the reported cases.

METASTASES of ENDOMETRIAL ADENOCARCINOMA

The metastatic pattern of endometrial adenocarcinoma has been extensively studied. This tumor has a progredient loco-regional spread, with a relatively low incidence of distant metastases. The distribution of the metastatic sites is, however, relatively at random. There is no preferential site, except with pulmonary and hepatic parenchyma, commonly involved in pelvic neoplasms.

The neoplasm originates from the surface epithelium, normally already somewhat anchored within the muscle layers of the myometrium. This enables cancers of the monolayered epithelium to penetrate relatively rapidly into the myometrium. After full penetration towards and through the serosa, cells can spread either along the pelvic lymphatics or within the peritoneal cavity or both. It is not unlikely that 'low-situated cancers', those more towards the cervix, would have more lymphatic extension than those at the fundus where more peritoneal extensions should be expected. This issue has, however, never been addressed and is indeed only supposition.

Autopsy Data - General Pattern

There are several reports, compared with other cancers, on autopsy data of patients who have died of endometrial carcinoma. The pathology at autopsy can be divided between intrapelvic and extrapelvic extension as in table 11.120 (Beck et al.).

These data immediately show the overwhelming preponderance of intra-pelvic spread, followed by some abdominal spread, particularly via the para-aortic nodes and encasement of small bowel. Except in the lung, there were almost no supra-diaphragmatic metastases. Bone also scores low. Transcoelomic spread is the major cause of death.

Table 11.120 -Endometrial Adenocarcinoma
Findings at autopsy in 36 cases (')
Data of Beck et al. 1963

Intrapelvic		Extrapelvic (present in80%)	
Cervix	25%	Abdominal	
Vagina	14	Liver	40%
Vulva	6	Adrenal	3
Tuba-Ovaries	48	Kidney	3
Parametrium	60	Pancreas	3
Pelvic periton.	66	Spleen	3
Urethra	3	ParaAortic nodes	62
Bladder	8	Inguinal nodes	3
Ureter	14	Bowel	34
Pelvic veins	8	Supra-Diaphragmatic	
Pelvic nodes	60	Lung	19%
		Mediastin.nodes	8
		Bone	8

(') all patients had been 'treated'.

There has been extensive discussion in the literature concerning ovarian and vaginal metastases. The above mentioned data indicate that about half of the patients will have ovarian involvement or metastases, contiguous progression, though it is important to realize that ovarian cancer can also progress towards the endometrium or occur as simultaneous development: 'field cancerisation'.
Invasion of the vagina undoubtedly occurs by means of lymphatic permeation. Nodular infiltration can occur as distant lymphatic spread and manifests itself more in the lateral caudal walls. A distinction is usually not made in the reports and also usually included along with the true recurrences in the vault.

Table 11.121 -Endometrial Adenocarcinoma
Findings at autopsy (N=88)
Data of Henriksen 1975

Node Station		Abdominal	
Hypogastrics	61%	Vulva	4%
Ext.Iliacs	48%	Vagina	25
Com.Iliacs	40%	Urinary Bladder	23
Obturator	37%	Ovary	34
Sacral	22%	Bowel	29
Para-Aortics	59%	Ureter	8
Para-Aortics only	15%	Peritoneum	39
Inguinals	16%	Spleen	14
		Kidney	10
Supraclavicular	12%	Adrenal	14
Mediastinal	18%	Liver	29
Axillary	5%		
Vertebra	20%	Lung	29%

Henriksen has reported on autopsy data on 188 patients. He remarked the large number of sites involved, but could not give particular explanation for this high variability. He humbly notifies, that it is impossible to cover every organ in every autopsy. The intrathoracal organs are the most frequently involved. In spite of the large number treated, he remarked ovarian metastases in 34% (tablel 11.121).

Analysing 48 patients dying with persistent malignant disease in a series of 155, De Muelenaere found that only 20% of the patients died following hematogenous spread. He categorized the data according to stage of disease at presentation (table 11.122).

Table 11.122 -Endometrial Adenocarcinoma
Cause of Death as seen at autopsy
Data of DeMuelenaere

Status of 48 dead patients of a series of 155	
Pelvic spread	25% of 48
Abdominal spread	44%
Hematogenous	21%
Unrelated, but cancer present	10%

Table 11.123 shows the data of Heberling et al. The similarity with the data of Beck et al. is very close and confirms the overall trend of pelvi-abdominal spread as the most important form.
Stage IV is assigned to patients with distant metasta-

ses at presentation. Reviewing 99 patients, Aalders reported on the metastatic pattern present. The data can be compared with autopsy data (table 11.124). Dating backto the a pre-US and CT-era, the low rate of liver metastases is obvious.

Table 11.123 -Endometrial Adenocarcinoma
Findings at autopsy in 165 patients
Data of Heberling et al.

Intrapelvic		Extrapelvic	
Cervix	14%	Abdominal	
Vagina	16	Liver	28%
Vulva	1	Adrenal	4
Tuba	5	Gallbladder	1
Ovaries	19	Kidney	5
Parametrium	42	Pancreas	3
Pelvic periton.	--	Spleen	5
Urethra	--	ParaAortic nodes	42
Bladder	13	Inguinal nodes	-
Ureter	20	GIT	24
Pelvic veins	--	SupraDiaphragmatic	
Pelvic nodes	--	Lung	26
		Mediastin.nodes	--
		Bone	23

Table 11.124 -Endometrial Adenocarcinoma
Metastases in Stage-IV- patients (N=99)
Data of Aalders et al. (1984)

Pelvi-Abdominal		Supra-Diaphramatic	
Bladder Mucosa	13%	Lungs	36%
Rectal mucosa	4	Supraclavicular No	5
Inguinal Nodes	(5)	Axillary	1
Ascites (cytol.+)	5	Brain	1
Liver	2	Multiple	23

Loco-Regional spread

The 'official' regional lymph node stations are the hypogastric (including obturator), external iliac, common iliac, presacral and para-aortic nodes. The UICC has codified N1 as evidence of any involvement in these nodes, 'closing the door' for anatomic categorization, as most authors will not make the distinction.

In a landmark publication, Creasman et al. have presented some data derived from a study of 140 stage I patients (table11.125). The incidence of positive nodes increases with stage, grading and muscle invasion.

Reviewing 159 stage I-II patients, Masubuchi et al. correlated anatomical involvement with stage and other variables (table 11.126).

In a study of 188 autopsies, Henriksen noticed that the lymphatic spread of endometrial carcinoma follows a less orderly pattern than that of cervical carcinoma. The pattern is less predictable, even suggesting at times an explosive propulsion of malignant emboli in all directions. The distal nodal and organ involvement at early stages must be a consequence of early blood vessel invasion. The (endo)-cervical involvement is correlated with a higher incidence of distant metastases than in comparable stages of cervical carcinoma.

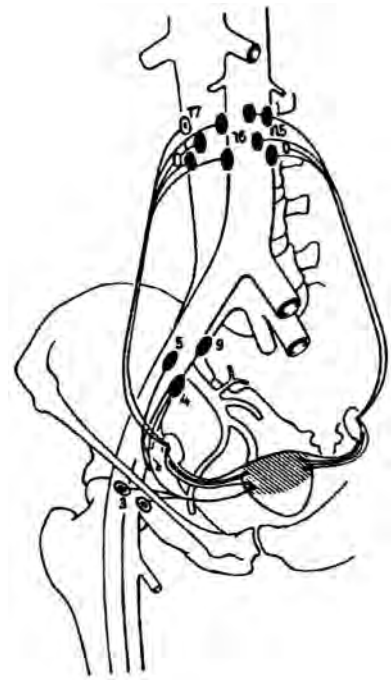

Fig.11.28 - Lymphatic drainage from the endometrium: 3: inguinal node; 4,5 external iliac nodes; 9 iliaca communis; 15,16,17 para-aortal and paracaval nodes (from Kremp et al., with permission)

Table 11.125 - Endometrial Adenocarcinoma
Regional Lymph node Involvement in Stage I (N=140)
Data from Creasman et al. 1976

	IA	IB	All
Pelvic Node positive	6.2%	18.0%	11.4%
Aortic node positive	3.8	11.7	5.7%

Table 11.126 - Endometrial Adenocarcinoma
Regional Lymph node Involvement in Stages I -II
Data of Masubuchi et al. 1979 (N=159)

Positive lymph nodes in 10/128 patients

	Positive	Endocervical	Ly.Perm.
Obturator	6	2/6	3/6
Hypogastric	4	1/4	4/4
Ext. Iliac	14	12/14	9/14
Parametrium	3	1/3	2/3
Inguinal	1	1/1	1/1

Note: Ly.Perm: lymphatic permeation

Para-aortic lymph node metastases were present in about half of the patients at autopsy. It would seem that, compared with other malignant tumors, the growth of these metastases remains localized, to the extent that they do not invade the organs situated in the back of the abdomen.

In stage I patients, para-aortic nodes were positive in 15% of the 74 patients in the series of Chen et al. When deep myometrial involvement is taken in account, it increase to 42.9%. They also found an increase when the involved tumor surface is taken in

account, but not according to the site within the uterus. Creasman et al. noted an incidence of 6% in 631 stage I (multi-centric) patients.
Similar results were reported by Hirahatake et al. on 200 patients. The incidence of para-aortic nodes increase significantly with myometrial invasion, cervical involvement, lymphatic space involvement and the presence of positive pelvic nodes. However, grade and adnexal involvement had no influence.
As mentioned previously, Henriksen made several interesting observations in the autopsies of 188 patients. In 15% the para-aortic nodes were involved in 15% with or without distant metastases. He stresses the fact that in the older age group, it is sometimes difficult to recognize some lymph nodes, in view of their atrophic nature, with fatty infiltration, fibrosis and other aging phenomena. He remarked that small tumor embolism lodged in any vessel could result in shunting or rerouting of lymph flow, so that an entire lymph node group could be bypassed.
Infiltration of the parametria is much less frequent than in cervical cancer. According to Tamussino et al., it occurs only when there is invasive spread with-in the cervix and is always continuous.

Non-Regional Lymph Node Metastases

One case has been reported by Ritota et al. in a F78 presenting four years after hysterectomy with obstructive jaundice. She was found to have a dense tumor in the paraduodenal and retroperitoneal region.
Inguinal metastases are not uncommon and tumor cells can reach this site along the round ligament. A patient aged 70 presented with a large inguinal mass occuring from a stage III endometrial carcinoma (Ramahi et al.).
Supraclavicular lymph nodes are not rare.

Distant Metastases

As already stated, distant hematogenous metastases are not frequent, but they can present in various insidious ways. In 631 stage I patients 6% already had extra-uterine non-nodal distant metastases (Creasman et al.).

Liver Metastases

Present at autopsy in about half of the patients, metastases in the liver have not received much attention in the literature as far as pathological data are concerned. Sato et al. have succinctly discussed the problem but had only two cases of liver metastases in their 197 patients.

Thoracal Metastases

At autopsy stated asaccountin for 20 to 26%, Ballon et al. found lung metastases in only 33 or 2.3% of their 1,434 patients. Multiple and bilateral metastases were present in 24, multiple and unilateral in 5. The lesion was single in 4 patients. In all patients, multiple other metastatic sites were present. Gilly et al. quote an incidence of 2.6% in 382 patients.
Radiological data were reported by Bouros et al. in 90 patients. The incidence of lung metastases was 5.8% in 1,550 patients (table 11.127).

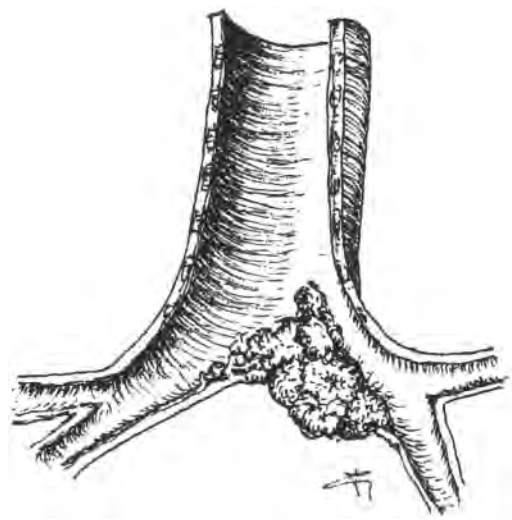

Fig.11.29 - Invasion of the Carina from a Mediastinal node metastatic from an Endometrial Carcinoma

Nodular pathology is the most frequent, with a large percentage of bilateral involvement. Pleural and mediastinal involvement would appear to be rare. The median interval from primary treatment to diagnosis of meta-stases was 25.5 months for solitary lesions. The size of the nodules varied from 4 to 105 mm.

One particularly notable case was reported by Beckert. It concerned a women presenting 10 months after hysterectomy, with fast progressive dyspnea, in whom chest radiograph showed multiple 'chicken-egg' great lung metastases. However, at autopsy mediastinal lymph nodes invasive in the main bronchi were found (fig. 11.29).

Table 11.127 -Endometrial Adenocarcinoma Chest Radiology findings (N=90) Data of Bouros et al.

Solitary lesions		18%
Multiple lesions		72%
Bilateral	61%	
Unilateral	11%	
Mass lesion		11%
Lymphangitis carcin.		3.5%
Pleural involvement		6.7%
Mediastinal nodes	(2 cases)	
Tracheal metastasis	(1 case)	

Brain Metastases

Cerebral metastases in endometrial adenocarcinoma are rare, but nevertheless, several case reports have

appeared (Table 11.128). The large majority are single metastases and no particular site seems preferential. Its rarity and somewhat dramatic presentation together with the present therapeutic possibilities have attracted more attention than previously.

Table 11.128 -Endometrial Adenocarcinoma
Metastases to the Brain - Literature reports

Author	Pat	Site	Interval
Salibi 1972	F67	FrontoParietal	7 mo
Nakano 1975	F77	Occipital Le	26 mo
Hacker 1980	F80	Brain stem	16 yrs
White 1982	F -	Supratentorial	--
Kishi 1985	F -	Supratentorial	--
Turner 1982	F 83	Frontal + dura	--
Ritchie 1985	F61	Multiple	Revealing
Sawada 1990	F43	Occipital Le	7 wks
Brezinka 1990	F59	Frontoparietal	1month
Kottke 1991	F59	Parietal Ri.	Revealing
Kottke 1991	F43	Frontal+Cerebell	Simult.
Kottke 1991	F46	FrontoParietal	Revealing
DePorre 1992	F74	Parieto-Occip.	6 mo
Wronski 1993	F70	Cerebellum	14 mo
Wronski 1993	F60	Multiple(')	3 mo
Ruelle 1994	F64	Cerebellum Ri	14 mo
Ruelle 1994	F63	Temporal Ri.	Revealing
DeWitte 1996	F40	Ri.Parietal	Revealing
Martinez 1998	F76	Occipital	18 mo

(') posterior third ventricle, left fontal, fossa posterior

A large series from one institute was reported by Cormio et al. Of 1069 treated patients, 10 or about 1% developed brain metastases. In 6 a single metastases was found. Overall, there were 3 patients with a cerebellar metastasis. At diagnosis, 6 patients had no other metastasis elsewhere.

One case of skull with dural metastases and subdural hematoma was reported in a patient F83 presenting with chronic metrorrhagias. A raised non-tender lesion was visible at the frontal region (Turner et al.).
Hargraves et al. have reported on a patient (F51) presenting with cauda equina syndrome. Laminectomy showed an intradural mass with metastatic adenocarcinoma. The uterine tumor was found subsequently.
Pituitary apoplexy was the presenting syndrome in a F71 due to a large pituitary metastases of an unknown endometrial carcinoma (Lieschke et al.).

Bone Metastases

Mentioned as occurring at a low rate in the autopsy series, bone metastases mainly present in the spine. In 382 patients, Gilly et al. found 6 with bone metastases or 1.6%.

Several particularly unusual sites have been reported, even as revealing metastasis (table 11.129). It must be noticed that they are almost all in the lower extremity, pointing to the possibility of some venous reflux from a 'blocked' pelvis.

Table 11.129 -Endometrial Adenocarcinoma
Bone metastases at unusual sites
Cases reported in the literature

Author	Pat.	Site	Interval
Vanecko 1967	F67	Ri.fibula shaft	14 mo
Vanecko 1967	F54	Le.fibula shaft	Revealing
Gelberman 1975	F64	Le tibia distal	4 mo
Brufman 1978	F69	Trochanter minor(')	simultan
Beller 1982	F59	Le femur distal	9 mo
Onuba1983	F57	Ri.Tibia(fracture)	Revealing
Litton 1991	F55	Ri.Calcaneum	2 yrs
Cooper 1994	F59	Ri.Calcaneum	Revealing
Schols 1995	F66	Ri.humerus shaft	18 mo
Petru 1995	F61	Le.Calcan.Talus	Revealing
Clarke 1996	F55	Ri.Calcaneum	18 mo
Malicky 1997	F44	Le femur proximal	Revealing
Rocha 2000	F67	Femur	>5 yrs

(') hypertrophic type

Reviewing bone metastasis in gynecological oncology, Abdul-Karim et al. found 17 patients with endometrial carcinoma. The involved sites are shown in table 11.130.

Table 11.130 -Endometrial Adenocarcinoma
Bone metastases in 17 patients
Data of Abdul-Karim et al.

Vertebrae	13	Femur	2
Pelvic Bones	2	Tibia	1
Ribs	1	Sternum	1

The pattern is similar to that reported previously by Heberling et al. They found metastases in the lumbar spine in 17% of the 165 autopsied patients and 12.7% in the thoracal vertebrae. The cervical spine was involved in 6%, the skull in 1.2%, the pelvis in only 3% and the femur in 2.4%.

Spinal cord compression at cauda equina due to destruction of the 5th lumbar vertebral body was reported in a woman of 78 by Kapp et al. They found three other cases in the literature.
Prior to the CT-era, Richter reported on a woman with slow progressive transverse lesion with incomplete paraplegia. A large infiltrative tumor was found to be destroying the distal lumbar vertebrae and invading extensively the spinal canal. This was probably a progressively invading para-aortic lymph node.

Gynecological Metastases

Metastatic involvement of the cervix, the vagina and the ovaries has been described and discussed.
Two pathways can be considered. The lymphatic spread from the myometrium to the ovary and the implantation of intraluminal tumor within the fallopian tubes and further towards the ovaries. The presence of intraluminal tumor is a strong argument in favor of the latter.
Considerable controversy has arisen about the significance of positive tubal cytology. In 99 stage I

patients with endometrial carcinoma, tubal cytology was positive in 48 patients. However, further analysis did not detect any significant influence on the prognosis, nor unfavorable events (Mulvany et al.).
Spread towards the cervix can be explained by submucosal lymphatic spread and determines the stage of the disease. Further spread towards the vagina has a similar pathway.
Ovarian involvement has been discussed in the literature. Its incidence overall varies from 5 to 10% depending on the series and probably also the criteria.
Simultaneously occurring endometrioid neoplasms are considered by Eifel et al. as separate tumors, while other histologies are considered as metastatic. More specific criteria have been proposed by Ulbright et al.:

1. a multinodular ovarian pattern;
2. small ovaries, less than 5cm;
3. bilateral involvement;
4. deep myometrial invasion;
5. vascular invasion shown;
6. involvement of the tubal lumen;
7. associated endometrial hyperplasia.

In 439 stage I patients, Takeshima et al. found 22, or 5% with ovarian metastases and should in fact be considered stage IV patients. This issue is not addressed in the UICC-TNM rules. The size of the metastases ranged between 1 and 100 mm. Bilaterality occurred in 3 or 14%. Several patients also had positive pelvic node and/or positive peritoneal cytology.
An incidence of 10% was reported in 514 patients and rose with myometrial involvement, grade and positive peritoneal washings. No data for more advanced stages have been reported.

Head and Neck Metastases

This is a rare occurrence in endometrial adenocarcinoma. The few cases are shown in table 11.131. We are aware of only one case metastatic to the maxilla.

Table 11.131 -Endometrial Adenocarcinoma
Head and Neck Metastases
Cases reported in the literature

Author	Patient	Site	Interval
Orlian 1971	F	Maxilla	??
Ritchie 1985	F61	Larynx	Simultaneous
Maxymiw 1991	F63	Mandible	4 mo
Baden1992	F78	Tongue	7 yrs
Scott 1998	F50	Ethmoid	3 mo
Dosoretz 1999	F71	Mandible	1 mo
Rocha 2000	F67	Mandible	5 yrs

Metastases to the Spleen

This very particular site has received somewhat more attention in the last decades, particularly for endometrial carcinoma (table 11.132).
In the study of Berge, splenic metastases were found in 3 of the 111 patients with endometrial carcinoma.
A woman presented a year after hysterectomy with dull pain in the left hypochonder. Imaging showed a solitary mass of 10 cm diameter in the spleen. Surgery confirmed its metastatic nature (Arend et al.).

Table 11.132 -Endometrial Adenocarcinoma
Metastases in the Spleen -Literature reports

Author	Patient	Symptom	Interval
Klein 1987	F66	---	5 yrs
Jorgensen 1988	F59	Fever	7 mo
Gilks 1989	F72	Pain	3 yrs
Arend 1992	F62	Pain	1 yr
Hamy 1995	F47	Follow-up	6 yrs
Giuliani '99	F58	Follow-up	16 mo

As distant metastases are somewhat rare, these metastases will most probably, attract attention by their symptomatology. Present CT will disclose more than previously, as many patients had other metastases and were then not worthwhile publishing.

Cutaneous Metastases

Endometrial adenocarcinoma surprisingly gives rise to metastases in the skin, at very variable sites (table 11.133). Several scalp metastases have been reported. Some sites probably attract patient's attention, whereas others will not, due to their location f.i at the their back.
Several patients also had other sites involved either at diagnosis or later. Note that in several patients, the diagnosis of cutaneous metastases was made within a few months, probably due to an aggressive 'variety' of endometrial cancer.

Table 11.133 -Endometrial Adenocarcinoma
Cutaneous metastases
Cases reported in the literature

Author	Patient	Site of M	Interval
Rasbach 1978	F53	Scalp	1 mo
Rasbach 1978	F68	Multiple	no data
Damewood '80	F57	Left calf	1 mo
Damewood '80	F53	Head (2x)	1 mo
Damewood '80	F69	Abdomen	3 yrs
Damewood '80	F58	Scalp (2x)	2 mo
Damewood '80	F68	Multiple	no data
Debois1982	F50	Scalp	4 mo
Debois1982	F56	Scalp	25 mo
Dias 1992	F73	Multiple	3 yrs
Spencer 1994	F80	Abdomen	7 yrs
Giardina 1996	F55	Skin of great toe	18 mo
Kushner 1997	F56	Scalp	15 mo
Mandrekas '99	F58	Skin of big toe	30 mo
Dekker 1999	F60	Left ankle (4x)	3 yrs

Other metastases

One case metastatic to the breast was reported by Yazdi in a woman of 56, one month after surgery.
Three years before admission for dysphagia, a woman of 71 was diagnosed as having an endometrial adenocarcinoma. A metastasis at the mid-esophagus was histologically confirmed (Zarian et al.).

We are aware of only one case metastatic to the eye. A 67 year old women presented 14 months after surgery with a 'change' at the iris of the right eye (Capeans et al.).
Morris et al. have reported on three patients between 73 and 74 years of age, all presenting first with ascites. This is surprising, as we are not aware of other similar reports. This is probably underreported.

Cardiac problems due to involvement has been reported in two patients.
Almost immediately after surgery, a woman of 67 complained of dyspnea and retrosternal pain. At echocardiography, a large right ventricular mass with tricuspid insufficiency was found. An endocardial biopsy confirmed its metastatic nature (Arnold).
Fifteen months after surgery, chemotherapy was started for multiple abdominal recurrences in a patient of 62. During treatment, she developed cardiac tamponade; a few weeks later pleural effusion with positive cytology was found (Hayashi et al.). This is probably not an uncommon situation in patients with widespread metastases.
One particularly unusual case was reported by Chow et al. Before surgery, a pace-maker was positioned in the apex of the right ventricle. One year later a large-dumb bell tumor was found occupying the whole right ventricular cavity, confirmed as metastatic adenocarcinoma at surgery. A very probable hypothesis was that the tissue reaction with fibrin deposition at the endocardium provided a nidus for implantation of tumor cells.

Causes of Death

The best data are those from Henriksen (table 11.134). Only half of the patients seem to have died from their cancer, while 14% die from another cancer.

Table 11.134 - Endometrial Adenocarcinoma
Causes of Death (N=188)
Data of Henriksen 1975

Cause unrelated to endometrium cancer (92)	49%
Other Primary 27/92	
Endometrial carcinoma	51%
(distant metastases, hemorrhages, renal complications, radiation complications)	

Overall Lesson

Endometrial cancer has a strong lymphatic spread pattern, while the distant metastases will be in 'classic' organs as well as in other ones rarely involved by other cancers.

METASTASES from TUMORS of the MYOMETRIUM

Tumors of the myometrium, a muscular structure, are sarcomas, though several other specific tumors such as mixed mullerian and others have been described. We will not deal with this aspect any further, limiting to the reported metastases.

Metastasizing Benign Leiomyoma

This is a rare condition, but several cases have been reported with pulmonary and other metastases with intracaval tumoral extension up to the right heart (see Chapter 1). It occurs mainly in premenopausal women and the tumor originates in the pelvic veins. It can grow further within the vena cava and in some reach cases the right atrium, with extensive filling of the right heart cavities.
The relatively young age of the patients should be noticed, especially compared with the age of patients with metastatic sarcomas (table 11.135).

Table 11.135-UterineMetastasizing Benign Leiomyoma
Cardiac Involvement reported

Author	Patient	Site	Interval
Ariel 1966	F40	Pulmo	2 yrs(?)
Pellillo 1968	F22	Pulmo	3 yrs
Kaszar 1988	F42	Ri.Atrium	Simult
Steinmetz 1995	F47	Cava -Ri.Atrium	Simult.
Takemura 1996	F45	Pulmo - Ri.heart	4 yrs
Abramson 1999	F49	Pulmo	12 yrs
Ling 2000	F41(')	Ri.heart	Simult
Tasdelen 2000	F57	Ri.atrium	3 yrs

(') pregnant 36 weeks

According to Ling et al., 37 cases have been reported of intracardial extension from a 'metastasizing' leiomyomatosis. In several cases, the diagnosis was simul-taneous.

Two theories have been proposed to explain its formation. Knauer has hypothesized that the tumor originates from smooth muscle cells of the venous wall, whose proliferation has been stimulated by estrogens.
Invasion of the venous system by leiomyoma cells was proposed by Sitzenfrey as early as 1911, but its mechanisms has still not been elucidated, but probably parallels invasion mechanisms of malignant cells.

Malignant Myometrial Tumors.

The metastatic pattern of uterine sarcoma has been reported by three authors (table 11.135). A more detailed study was published by Rose et al., concerned 73 patients (table 11.137).
These data show the widespread metastatic pattern sarcomas usually have. Remark also the quite high number of metastatic lymph nodes up to the neck, so that a retroperitoneal pathway as described for testicular cancer should occur in this pelvic tumor too.
The authors found no significant difference according to histology type. The distant metastases in the lungs, the brain and other sites were independent of

intraperitoneal disease, in accordance with a pattern of hematogenous spread different from taht of lymphatic spread from within the pelvis.

Table 11.136 - Sarcoma of the Uterus
Metastatic Pattern

	Fleming(') 1984 N=22	Schwartz(") 1985 N=71
Pelvis		25.3%
Pelvic peritoneum	21	
Vagina	15	
Retroperitoneal	13	
Upper Abdomen		36.6
Peritoneum +diaphragm	21	
Serosa of bowel	16	
Liver	9	22.5
Pancreas	4	
Kidney	3	2.9
Spleen	3	
Adrenal	1	
Extra-Abdominal		
Lung	10	33.8
Esophagus	2	
Brain	2	
Breast	1	
Bone	1	8.6
Mandible	--	(1 case)

(') autopsy data
(") clinical, pathology and autopsy data

Nodal spread is certainly frequently present, even in stage I sarcomas of the uterus. Chen reviewed the literature at that time (1989) and found that pelvic nodes were present in 39% of the patients and aortic (retroperitoneal) in 30%.

Table 11.137 - Sarcoma of the Uterus
Metastatic Pattern - Data of Rose et al. (N=73)

Pelvi-Abdominal		Supra-Diaphragmatic	
Pelvic nodes	40.8%	Skin	9.6%
Abdominal N.	37.5	Breast	0
Peritoneum	58.9	Pericard	5.4
Stomach	4.1	Heart	4.1
Small Intestine	27.3	Pleura	28.7
Large Intestine	26.0	Lungs	52.0
Pancreas	6.8	Trachea	1.3
Liver	34.2	Thymus	3.0
Ovary	21.8	Neck nodes	4.1
Adrenal	15.0	Thoracic nodes	23.6
Kidney	4.1	Thyroid	4.1
Ureter	23.6	Bone	23.2
Spleen	9.5	Brain (')	8.2

(') cerebrum, cerebellum, medulla, meninges

The most frequently reported histology type is leiomyosarcoma.
Reviewing 28 cases of metastatic uterine leiomyosarcoma, Jones et al. found an average disease-free interval of 3.7 years, ranging from 3 months to 9 years. The most common site of metastases was the lung (13/28), while in 12, metastases were present in the pelvic peritoneum and distant in another 12. In four, only distant metastases were observed.

Table 11.138 -Leiomyosarcoma of the Myometrium
Case Reports on Distant Metastases

Author	Patient	Site of Metastases	Interval
Keir 1978	F48	Right ventricle	11 yrs
Kaku 1981	F31	Right heart	4 yrs
Broderick 1981	F49	Subcutan.Plantar	7 yrs
Kaziro 1981	F59	Tongue	8 yrs
Martin 1983	F30	Right Ventricle	3 mo
Alessi 1985	F64	Skin back scalp	16 mo
Lang 1985	F??	Left Atrium	5 yrs
Patanapan 1985	F31	Tigh-Buttock -Iliac bone	3yrs
Moreno 1987	F44	Left Ventricle	16 yrs
Hoy 1988	F58	Right ventricle	6 mo
Cruickshank'88	F30	Thyroid gland	17 mo
Warren 1990	F53	Endobronchial	7 yrs
Warren 1990	F40	Endobronchial	6 yrs
Prussia 1992	F36	Brain Parietal	9 yrs
Weh 1993	F35	Right ventricle	9 yrs
Arnouk 1993	F52	Pleura-Lung	Type 1
Takemori 1993	F47	Vertebra T8	??
Allen 1993	F65	Lip	3 yrs
Gerst 1993	F48	Endobronchial + small intestine	8 yrs
Wronski 1994	F60	Lung -Left parietal	5.5 yrs
Bourlaud 1995	F50	Pleura- Lung	Type1
Sidani 1996	F64	Small intestine	3 wks
Bateman 1997	F60	Breast	6 yrs
Tulasi 1997	F41	Breast	5 yrs
Saiz 1998	F49	Parotid	Type1(°)
Rao 1998	F63	Lung - Abd.Skin	1 yr
Nanassis 1999	F46	Spine T5-T6	3 yrs
Botwin 2000	F50	SpineT11, L3,Sacr	4yrs

(°) metastasis excised 6 years before.

Case reports with various metastatic sites from this uterine tumor have been reported (table 11.138). Several are late-occurring tumor thrombi within the vena cava, extending from the iliac vein up to the right ventricle through the tricuspid valve.

Akiba et al. reviewed the literature on endobronchial metastases from uterine sarcomas. They found 15 cases of which 6 had pulmonary metastases, 4 intra-abdominal metastases and 2 with bone metastases.
Endobronchial metastases are claimed to have been reported in 17 other cases of uterine sarcomas, of which 8 had a leiomyosarcoma. The other ones had various histologies.
Distant metastases from other sarcomas of the myometrium have also been reported (table 11.139).

Pulmonary metastases from sarcoma are, due to their slow growth, low number and good accessibility, a well-known appropriate indication for resection. Such series offer the opportunity to learn more on pathological data relating to the parenchymal metastases. Levenback et al. reported on 45 patients with uterine sarcomas. Although undoubtedly skewed to-wards operability, their data are interesting (table 11.140).

Table 11.139 -Sarcoma of the Myometrium
Case Reports on Distant Metastases

Rhabdomyosarcoma			
Goldstein 1999	F73(')	Mediastinal	11 mo
Mixed Mullerian Sarcoma			
Papadimitri 1989	F70	Esophagus	4 yrs
Iqbal 1993	F51	Frontal lobe	6 mo
Spraul 1997	F66	Iris + Ciliary Body	4 yrs
Cormio 1997	F48	Brain multiple+ Epidural + vertebra	5 days
Guidozzi 2000	F46	Omental cake	Simult
Guidozzi 2000	F49	Omental cake	Simult
Guidozzi 2000	F29	Mult.Vaginal	Simult
Endometrial stromal sarcoma			
Vargas 1990	F25	Intracardiac	1 mo
Phillips 1995	F52	Intracaval- Atrial	4 yrs
Debing 1998	F63	Intracaval	16 yrs
Osteosarcoma			
Akiba 1994	F73	Endobronchial	20 mo

Table 11.140 - Uterine Sarcoma
Pathology of Lung Metastases (N=45)
Data of Levenback et al.

Unilateral		71%
Number of nodules	One	51%
	2-5	33%
	>5	16%
Size of nodules	less than 2.1cm	31%
	more than 2 cm	69%

A rare histology type of uterine sarcoma is carcinosarcoma. Sreenan et al. reviewed 29 metastatic cases, of whom 17 originated from the myometrium. Metastases were present mainly in the pelvic cavity and abdomen, but several metastatic lymph nodes, metastases in the vagina, brain and breast were also observed.

METASTASES from CARCINOMA of the UTERINE CERVIX

The majority of cancers of the uterine cervix are of the epidermoid type. Adenocarcinoma in this site has, however, become somewhat more frequent in recent decades. They must of course be differentiated from an extension of an endometrial carcinoma. The distinction is not always clear in the reports.

Metastatic Pattern - Autopsy Data

Cancer of the uterine cervix first become 'invasive' when it invades the basal layer of the mucosa, entering lymphatic and intermuscular spaces, from where it spreads toward the regional lymph nodes. Further evolution takes place within the pelvic tissue, the parametria in particular and toward the neighbouring pelvic organs.

Distant extrapelvic metastases are common, more than for the endometrial cancers.

At autopsy, metastases from uterine cervical carcinoma will be found almost everywhere. This is well illustrated in the figures published by Henriksen as far back as 1949, obtained from a study on 154 non-treated and 202 treated patients (fig. 11.30).

Table 11.141 - Cancer of the Uterine Cervix
Metastatic Pattern (278 autopsies)
Data of Badib et al.

No metastases found in 27%
Metastases found in 203 patients (73%)
Only one distant metastases in 18 patients
Multiple distant metastases in 185 patients

Pelvic Nodes	14.0%	ExtraPelvic nodes	12.9%
Pelvic and other	45.6	Breast	1.4
Peritoneum	11.1	Pericard	2.9
Stomach	3.6	Heart	3.2
Small intestine	9.0	Major vessels	11.9
Colon	11.1	Pleura	14.4
Pancreas	5.8	Lungs	33.0
Liver	27.4	Upper resp.tract	1.4
Biliary tract	3.2	Upper GI tract	2.5
Spleen	4.7	Thymus	2.9
Adrenal	10.4	Thyroid	2.8
Diaphragm	13.7	Pituitary	0.3
Kidney	8.3	Brain	3.2
Bones	15.1	Spinal cord	0.7
Muscles	7.6	Meninges	4.3
Skin	3.6		

Table 11.142 - Cancer of the Uterine Cervix
Metastases distribution in 341 patients
Data of Carlson et al.

Site	Single N=110	Multiple N=231
Extrapelvic N	30.0%	68.0%
Supraclavic	N=9	N=57
Paraaortic	12	54
Inguinal	8	43
Iliac	1	28
Mediastinal	1	37
Cervical	1	16
Axillary	0	12
Other	1	38
Lung	36.3%	37.2%
Bone	16.3	29.0
Abdomen	7.2	41.9
Generalized	--	N=37
Peritoneum	N=2	11
Liver	6	42
GIT tract	0	24
Other	0	54
Various	10.0	43.0

The most frequently involved site is the liver along with the bones, the lungs and the small bowel. The other sites are all over the body and cover distant lymph node stations such as the cervical, the supraclavicular and the axillary nodes. Metastases as remote as the pituitary gland, the parotid and many other are

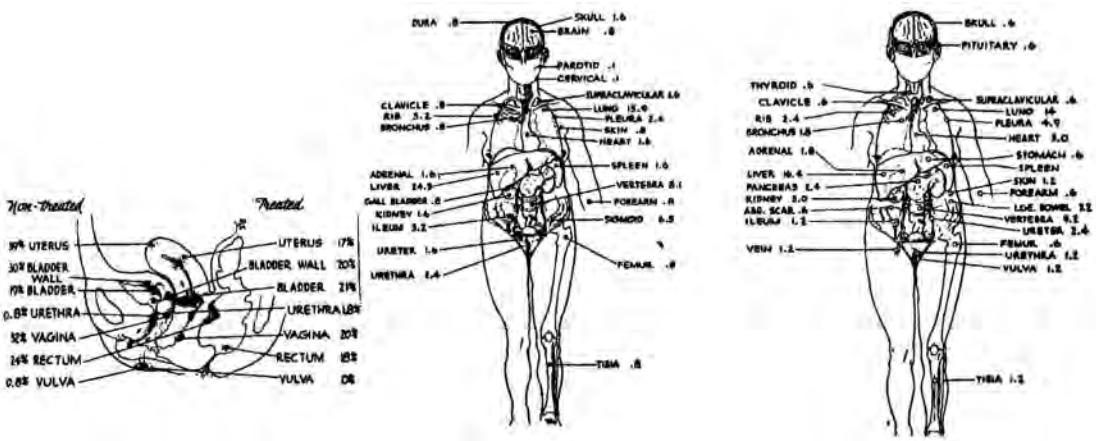

Fig.11.30 - Incidence of organ involvement observed in patients with cerix uteri carcinoma (154 non-treated and 202 treated): left : intrapelvic, middle: distant metastases in non-treated; right: in 202 treated patients (from Henriksen, with permission).

usually not apparent in vivo.
Another detailed study was done in 278 patients who have died after the diagnosis of cervical cancer (Badib et al.). (table 11.141).
Interesting clinical data were provided by Carlson et al. on 2220 patients, of whom 341 developed metastases. The site distribution differed somewhat between those with only one or more site involved. Abdominal and bone metastases were clearly more frequent in patients with multiple organ involved (table 11.142). More went probably undetected, as only few necropsies were performed.

Examining the influence of histology, Drescher et al. found a higher incidence of involvement for adenocarcinoma in para-aortic nodes, uterine corpus and the adrenal gland. Ascites and pleural effusion was also more common in this patient group.

Lymph Node Metastases

Cited as regional lymph nodes are
the parametrial
the hypogastric, including the obturator
the external iliac
the common iliac
the presacral
the lateral sacral nodes.
The para-aortic nodes are considered to be juxtaregional nodes.

Positive regional nodes are coded N1, while positive juxtaregional nodes are coded N4. Lymph node metastasis location is almost never considered in surgical series.

Para-Aortic Lymph Nodes

Compared with the lymphatic drainage from the endometrium, the drainage from the cervix occurs to a greater extent through the caudal lymph channels.

Table 11.143 - Cancer of the Uterine Cervix
Pelvic node involvement - Data of Noguchi et al.

Stage	N	Positive	Percent
IB	218	36	16.5%
IIA	101	32	31.7%
IIB	239	81	33.9%
IIIA	24	11	45.8%
IIIB	45	26	57.8%

Site	Node Number	Positive	Percent
Parametrial	96	24	25.0%
External Iliac	3275	144	4.4%
Internal Iliac(')	3619	250	6.9%
Obturator	2810	139	4.9%
Inguinal	1134	7	0.6%
Sacral	29	1	3.4%

(') hypogastric nodes

The lymphatics draining the uterine cervix form prominent lymphatic trunks flowing primarily to the external iliac, hypogastric, obturator and common iliac nodes. The less prominent channels flows towards the gluteal, the sacral and subaortic lymph nodes. There are also some smaller but consistent anterior and posterior channels behind the bladder and terminating in the iliac nodes at the lateral pelvic wall. The posterior channels course along the utero-sacral ligaments and turn cephalad. Some channels go to the superior rectal and other ones bypass the latter to the subaortic nodes. This results in three possible routes to the para-aortic nodes (fig. 11.32 and fig. 11.33):

1. the posterior cervical trunk directly to the para-aortic nodes;
2. after progressive involvement of pelvic nodes;
3. via the sacral and subaortic nodes to the para-aortic nodes (Buchsbaum). Data on the involvement of the different lymph node stations within the pelvis are scanty, and are usually reported as 'pelvic nodes'.

The data of Noguchi et al. were obtained from 627 cases, ranging from stage I to IIIB. Their results are in table 11.143. The data clearly show that the involvement increases with stages and that the most commonly involved station is likely to be the hypogastric group.

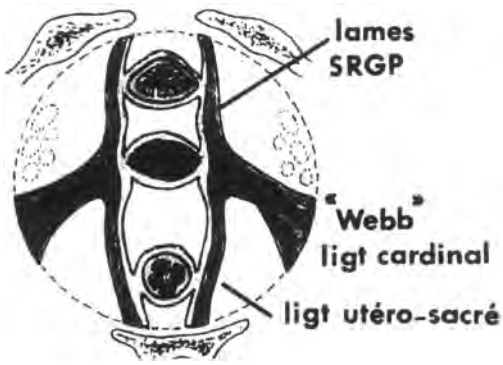

Fig.11.31 - Ligaments of the pelvic floor at the level of the cervix. (Pujol et al., with permission)
(SRGP: sacro-recto-genito-pubic band)

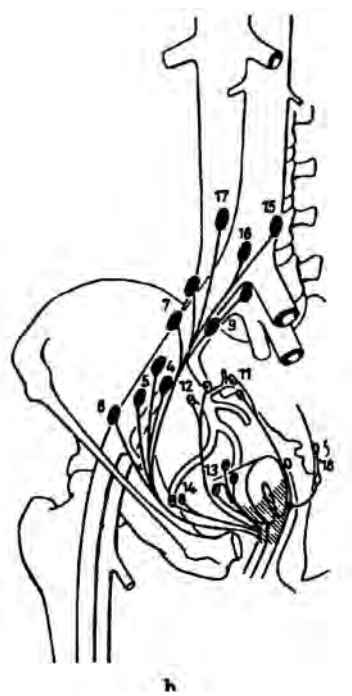

Fig.11.32 - Lymphatic drainage from the uterine cervix: 4,5,6 external iliac nodes; 7,9 common iliac, 11 lateral sacral; 12,13 gluteal group; 14 along art.obturatoria; 15,16,17 para-aortal and paracaval nodes; 18 rectal nodes. All 'black nodes' are visible on pedal lymphography (from Kremp et al., with permission)

The involvement of the different lymph node stations according to stage of disease has been examined by Benedetti-Panici et al. (table 11.144). Their study has revealed that the involvement does not differ according to stage, but that stage is in fact more a reflection of the parametrial and pelvic tissue by the primary tumor invasion front. Paracervical tissue is the major route for lymphatic spread. The most frequently involved stations are those above the obturator nerve, between iliac bifurcation, around the external iliac vein and artery and above the common iliac vessels (superficial obturator, external and common iliac).

Table 11.144 - Cancer of the Uterine Cervix
Lymph Node Stations involved
Data of Benedetti-Panici et al.

	Stage IB-IIA N=14	Advanced N=38
Common Iliac Superf.	28%	29%
Common Iliac deep	7	13
External Iliac	29	21
Obturator superior	86	92
Obturator deep	7	5
Parametrial	29	16
Internal Iliac	15	8
Presacral	15	3

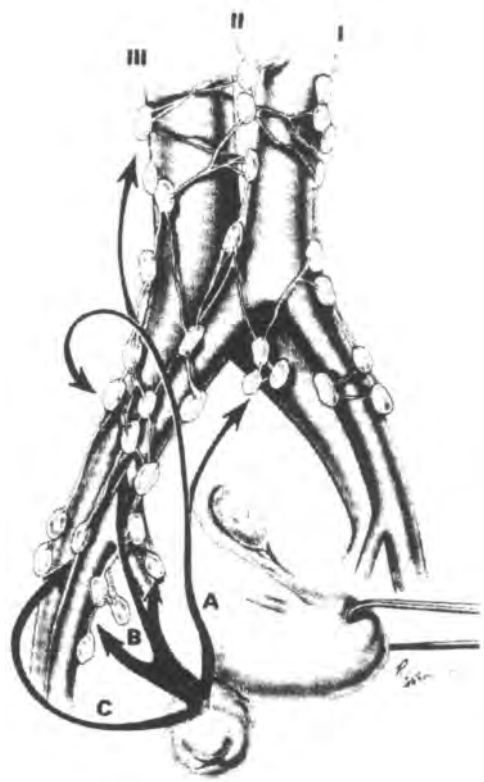

Fig.11.33 - Lymphatic drainage of the uterine cervix. A: posterior channels; B Major lymphatic channels directed laterally to the obturator, hypogastric and common iliac nodes; C: anterior channels terminating in the external iliac nodes. The three para-aortic lymph chains are I: left aortic; II aorto-caval and III caval (from Buchsbaum, with permission)

Considered as juxta-regional nodes, the involvement of the para-aortic (table 11.145) node has been examined by a number of authors. The latest reported data

are from Michel et al. (table 11.146).

Table 11.145 - Cancer of the Uterine Cervix
Incidence of Para-aortic node involvement
Data of Michel et al.

Stage	N	Pelvic+	Para-Aortic+ Pelvic +
Stage IB	299	23%	6%
Stage II	80	22%	12
Stage IIA	23	12%	0
Stage IIB	57	25%	16
Size <2 cm	136	14	3
2-4 cm	98	14	7
>4 cm	187	24	11
Epidermoid	361	19	8
Adenocarcinoma	60	18	7

Table 11.146 - Cancer of the Uterine Cervix
Incidence of Para-aortic node involvement (N=379)
Data of Michel et al.

Additional data	
Para-aortic involvement	8%
Pelvic and para-aortic positive	26%
Isolated para-aortic positive	0.9%
Para-Ao+Ext.Iliac+Comm.Iliac	3%
Common Iliac + Para-Aortic positive	0.5%
Intercavo-aortic	3%
Left para-aortic chain	5%
Paracaval	1%
Presacral	2%
Supra- inframesenteric	3%

Metastases to the solar area, the greater splanchnic nerve plexus, between the fourth and the tenth thoracic segments are not uncommon, but are rarely addressed in the literature. Thirteen cases were reported by Diddle. The symptomatology consists of progressive dyspepsia, anorexia and epigastric distress and ends usually in high intestinal obstruction or cachexia.
As these report dates back to the pre-CT era, but in these patients it would seem to correspond to retroperitoneal, even retrogastric masses, as discussed further.

Non-Regional Lymph Nodes

We found only one case mentioning a large ulcerated inguinal node in a patient late in the evolution. She also had multiple other metastases (Böhme et al.).
Metastases in the left supraclavicular node are a common occurrence during the later stages of evolution. Cells coming from the para-aortic nodes migrate toward the mediastinum and further along the ductus lymphaticus to the left supraclavicular node when a degree of reflux occurs in the joining veins (see Chapter 7).

As far back as 1972, Diddle et al. reported on 18 cases from 746 women dying of cervical cancer. In 3 of them there were no other lesions found in the regions below the diaphragm nor in the mediastinum. Cells must pass along the node stations directly to the supraclavicular region (skip-metastases).

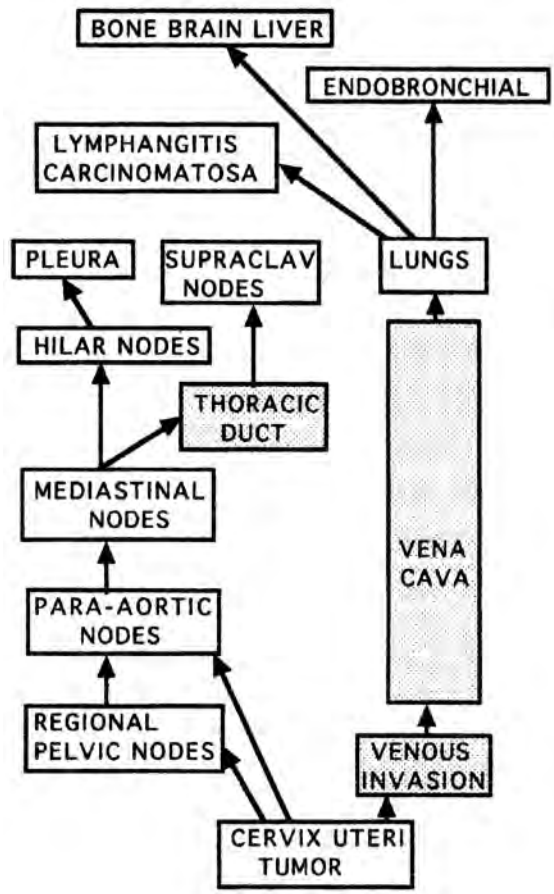

Fig. 11.34 - The dual pathway of metastatic spread from a cervical carcinoma.

Surgical 'pre-treatment' exploration of the scalene nodes has yielded information on the incidence of involvement of these nodes. Manetta et al. reviewing the literature found that these nodes were involved (by scalene biopsy) in 38/344 or 11.0% patients with advanced cancer and 13 of 132 or 10% of patients with recurrent cancer. In 24 patients with advanced cancer, none of the patients had a positive scalene biopsy. On the other hand, Vasilev et al. found 4/17 or 23.5% to be positive.

Distant Metastases

Additionally to the already discussed lymphatic pathway, the spread of a cervical tumor follows a classical hematogenous pathway. Both are, however, not mutually exclusive (fig. 11.34).
As seen in the previous tables, liver, lung and abdominal (peritoneal) metastases are the most frequent. There are more reports on uncommon metastases than about the usual sites.

Liver Metastases

Although cited in the autopsy reports as occurring in about 30% of the patients dying of cancer, very little information is available in the literature concerning their incidence during evolution of the patients after diagnosis. We found only a recent report of Kim et al. From a series of 1,665 patients, only 20 patients (1.2%) developed liver metastases at presentation or during follow-up (table 11.147).

Table 11. 147 - Cancer of the Uterine Cervix
Data on Liver metastases in 20 patients
Data of Kim et al.

Liver metastases isolated	1/20
with other sites	19/20
With persistent or recurrent pelvic	13/20
With extra-regional lymph nodes	11/20
With extra-hepatic metastases	16/20
At initial presentation	2/20
Pattern	
Less dense than parenchyma	18/20
Solitary in one lobe	4/20
Multiple	16/20
Multiple in both lobes	11/20
Single or more in one lobe	9/20
Tumor size larger than 4 cm	14/20

Some unusual cases have been reported. Three years after first treatment of a stage IIA, the patient presented with an acute episode of abdominal pain and sensitive right hypochonder. Emergency CT showed a subcapsular hematoma due to spontaneous hemorrhage of a known hepatic metastasis (LaFianza et al.).
Multiple cystic hepatic metastases were described in a patient 7 years after first treatment (Esterman et al.).

A patient (F38) presented with obstructive jaundice due to a large posterolateral hepatic mass obstructing both bile ducts (Raggio et al.). There were no retroperitoneal lymph nodes nor mass.
In a patient presenting with cholecystitis, an extensive single metastatic infiltration was found in the gallbladder (Bicher et al.).

Thoracic Metastases

Without stating the total number of patients treated, Shin et al. reported the findings on imaging in 62 patients with thoracic metastases of any type. In 71% pulmonary metastases were present, but some lymphadenopathy was found in 32% and pleural effusion in 27%. Several patients had more than one type of metastatic involvement (table 11.148).

Remarkable is that much more pleural effusion was noted at the right side. In two cases, a vena cava superior syndrome was observed.
Data on the incidence have been reported by Imachi et al. In a series of 817 patients, 50, or 6.1%, developed pulmonary metastases In 42% of them, they were asymptomatic. Within two years of diagnosis 96% of all lung metastases were found. The incidence correlated with stage (Stage 1:1.5% vs. stage IV: 21%) and histology (non-keratinizing epidermoid 9.1% and adenocarcinoma 11.6%).

Table 11.148 -Cancer of the Cervix Uteri
(Squamous cell)
Thoracic Metastatic Pattern in 62 patients
Data of Shin et al.

Parenchymal Lung Nodule		71%
Nodular Multiple	29/44	
Nodular Solitary	7/44	
Cavitary	4/44	
Reticulo-nodular	4/44	
Lymphadenopathy Any		32%
Mediastinal	7/20	
Hilar	7/20	
Both	6/20	
Pleural Effusion and metastases		27%
At right	12/17	
At left	3/17	
Bilateral	2/17	
Chest wall metastases (ribs-spine)		6%
Endobronchial metastases		5%
Lymphangitic carcinomatosa		3%

Bilateral involvement was seen in 44%, mostly with a multiple nodule pattern. In 40% of the adenocarcinoma patients with lung metastases, it had the aspect of a pneumonia. Sputum cytology was positive in 30% of the epidermoid patients while none was positive in the adenocarcinoma patients.

Later on 2,116 patients, of whom 88 or 4% developed pulmonary metastases, Barter obtained similar data. In a series of 1,332 cases, metastases to the lung were detected in 40, or 3.0% (Gilly et al.). An increase depending on stage of the primary was noted, as evident in the data of D'Orsi et al. (table 11.148).

Table 11.149 - Cancer of the Uterine Cervix
Incidence of Pulmonary Metastases according to stage
Data of D'Orsi et al

Stage I	4/101	4.0%
Stage II	6/95	6.3%
Stage III	1/53	1.9%
Stage IV	6/55	10.9%

Reviewing the clinical records of 304 patients with cervical cancer, either adenocarcinoma or epidermoid, Sostman et al. found a higher number of any metastases in the adenocarcinoma group (20%) than in the epidermoid group (4%). In adenocarcinoma only pulmonary nodules were seen, whereas in epidermoid cancers, 4/14 had lymph node metastases and 3/14 had effusion. In six, pulmonary nodules were seen.
A rare cavitary (necrotizing?) pulmonary metastasis in the upper lobe was observed 4 years after first treatment in a F37, but further follow-up was not done (Kirubakaran et al.).

According to the data of Shin et al., lymphangitis carcinomatosa would appear to be very rare. One case has been reported in a F44 stage IIIB epidermoid six months after diagnosis (Kennedy et al.). A women of 31 presented with profuse vaginal bleeding, dyspnea and non-productive cough. A chest roentgenogram showed multiple bilateral reticulonodular infiltrates, but further exploration also showed multiple other metastases (Perez-Lasala et al.). Three cases were reported by Buchsbaum. The interval between first diagnosis and the lymphangitis ranged from 3 to 14 months.

Spontaneous pneumothorax was reported in one patient (F58) with multiple cavitary pulmonary metastases four years after surgery for a carcinoma of the cervix (Tawney et al.). No other similar case for this primary has been reported.

Endobronchial metastases are rare, about 5%. A patient has been reported in whom it was detected at staging due to a lingular infiltrate. The patient was a smoker. (Kennedy et al.). Other singular cases have been reported. The incidence is probably underestimated, as endoscopy is not always performed. The delay for endobronchial metastases is relatively long (28 months) (Schraub et al.).
As histology of most bronchial cancers and cervical metastases is the same, problems can arraise in relation to differential diagnosis. The radiological aspect, absence of smoking and the short delay after first treatment are indicative of metastases rather than of a new primary.

Diffuse intrapulmonary tumor embolism was the cause of death six years after surgery in a M62. Tumor cells were seen exclusively in the alveolar septal capillaries; the arteries, arterioles and lymphatic vessels being free (Soares et al.).
The rare situation of metastatic chylothorax was mentioned in a F52 with cervical cancer, without further details (Browse et al.).
Severe bronchorrhea revealed a metastatic long mass from a cervical adenocarcinoma in a F40 (Epaulard et al.).

Gynecological Metastases

While involvement of the Fallopian tube in endometrial cancer can be considered logical, this is less the case in cervical cancer. Anbrokh et al. have reported a study of 221 patients. They found metastatic involvement in 8 patients (12 tubes) or 3.5%. We are not aware of similar studies, since this was reported in 1975.
Böhme et al. reported on a metastasis in the clitoris, during the malignant evolution of the cancer in a patient (F52) treated for a Stage III tumor.
Ovarian metastasis has been much discussed in the literature. Its incidence is very low. We have compiled some data in table 11.149.

Table 11.149 - Cancer of the Uterine Cervix
Ovarian metastases at surgery
Literature data

Author	N	Hist	Stage	N	%
Baltzer 1981	749	Epid	IB-II	4	0.5
Tabata 1987	278	Epid	IB-III	0	--
	48	Adeno	IB-III	6	12.5
Sutton 1992	770	Epid	IB	4	0.5
	121	Adeno	IB	2	1.7
Brown 1990	107	Adeno	I	1	1
Toki 1991	524	Epid	I	1	0.19
	36	Adeno	I	2	5.5
Wu 1997	1,507	Both	I-III	10	0.06
Natsume 1999	40	Adeno	IB	1	2.5
	5	Adeno	IIA	1	20
	37	Adeno	IIB	7	18.9

There has been some discussion about the pathways from the cervix to the ovary. Eight of the ten cases of Wu had stromal metastasis, indicating a lymphatic route as the ovary is known to have communicating channels with the pelvic lymphatic chains. The surface metastases are probably also lymphatic, at least in cervical cancer.
Only half of the reported patients with ovarian metastases from cervical cancer also have positive lymph nodes (review by Wu et al.).

The incidence of ovarian metastases in adenocarcinoma is much higher than in epidermoid carcinoma. There is an explained increase in incidence in the more recent reports.
One patient was reported by Marais et al. where the ovarian metastasis was the first clinical sign and at pathology, a cervical cancer was found.
Cassidy et al. have reported on a young woman treated for a stage I squamous cancer and presenting 16 months later with a small vaginal and a significant ovarian cyst which at histology was found to be a metastasis.
The low incidence of ovarian metastases would seem a justification for restricting surgery to simple hysterectomy, but cases of ovarian metastases occurring afterwards have been reported (Young et al.).
Oophoropexy has also been proposed. Nguyen et al. have reported, however, on ovarian metastasis occurring 8 years later in such a transposed ovary.

Abdominal Metastases

In view of the frequent involvement of the abdominal cavity, peritoneal cytology has been examined in a few series in order to obtain an insight into 'invisible' intracavitary spread.

Its efficiency seems low. Of 109 patients subjected to this procedure, only 9 had positive cytology; 5 at first diagnosis and 4 recurrences. Unfortunately the total number of patients treated was not given, so that the true incidence cannot be determined. There were more positive cytologies in adenocarcino-ma patients (3/18

or 16.7%) than in epidermoid patients (4/82 or 4.9%) (Zuna et al.).

Lymphatic metastases in the retroperitoneal space can lead to growths that will invade the neighbouring structures. An invasion of the duodenum as may occur in testicular and other cancers can occur also in cervical cancer. This type of invasion must be differentiated at least 'academically' from true metastatic lesions. A distinction is, however, never made in the reports on metastases towards the stomach and the duodenum.
A case of duodenal invasion from a retroperitoneal mass was reported in a 64 year old woman. The diagnosis was postponed for months as being a duodenal ulcer (Gurian et al.).
An aorto-duodenal fistula was found at autopsy in a 36 year old woman presenting after passing grossly bloody stools. An irregular encasement of the aorta, of the superior mesenteric artery and of the duodenum was found at imaging, and at laparotomy. At autopsy a massive necrotic retroperitoneal mass was uncovered (Geary et al.).

Several lumbar vertebral metastases originate from an invasion of the body from massive lymph nodes (Fisher et al.). (see further)
In the same group, we can place invasion of the psoas muscle, a rare occurrence but probably underdiagnosed in cervix uteri patients. A woman aged 50 has been reported with massive metastases of the psoas with destruction of the iliac bone (Bar-Dayan et al.). Correlated with psoas invasion is the situation of lumbar or lumbosacral plexopathy. Hardly mentionned as occurring in cervix cancer patients, Saphner et al. saw this complication in 25 patients in a series of 1,219 (chapter 7).

A bile-duct obstruction coming from a retroperitoneal mass to the region of the porta hepatis was described by Abu-Ghazaleh et al., who also reported on two other patients with duodenal problems caused by para-aortic nodes.

Brain Metastases

Metastases in the brain are rare. In the autopsy series, they account for 2 to 5%. Nevertheless, several cases reports have appeared.
In a series of 1,219 patients (stages I-IV), only 6 patients were found to have brain metastases (Saphner et al.).
A literature review in 1997 by Robinson et al. found 66 reported cases. The interval from first treatment to diagnosis of the metastases ranged from 0 to 8 years, with a mean of 30 months. Almost all were single metastases.

We are aware of two reports on the rare cerebellar metastases. A woman aged 46 was diagnosed as having a cerebellar metastases 11 years after a stage II treatment (Esterman et al.) and calcified cerebellar metastases was diagnosed in a woman aged 57, two years after first treatment (Petiot et al.).
An intramedullary spinal metastasis was reported in a patient aged 29, at the level of cervical 4, a few months after treatment for a stage IB (Amin).
Carcinomatous meningitis is also rare in cervical carcinoma. According to Aboulafia et al., three cases have been reported. All had many other meta-static sites and had a short survival. The interval between first diagnosis and the meningeal problem is usually short. It amounted to only six weeks in the case (F53) reported by Weithman et al.

A peculiar case presenting with hemiballism was recently reported in a 38 year old woman, 4 months after treatment of a stage IBB. Hemiballism is a rare mo-vement disorder characterized by involuntary large amplitude movements of the limbs on one side of the body. CT disclosed a solitary lesion in the left cerebral peduncle extending into the inferior aspect of the basal ganglia complex (Ziainia et al.).

Ophthalmic Metastases

A few cases have been reported. This seems very rare in cancer of the cervix (table 11.151).

Table 11.151 - Cancer of the Cervix Uteri
Ophthalmic Metastases - Literature Reports

Adenocarcinoma				
Planten 1981	F82	??	Ri.iris	6 yrs
Wiegel 1995	F25	IB	Le.choroid	2 yrs
Epidermoid				
Kurosawa 1987	F54	??	Ri. iris	6 mo
Ortiz 1995	F28	II	Subconjunctival	21 mo
Lee 1997	F46	IIB	Ri.orbita	6 mo
Inoue 2000	F55	IIIB	Bilat.Choroid	7 mo

Cardiac Metastases

Several case reports have appeared (table 11.152) of patients presenting with cardial or pericardial metastases during follow-up and in two patients diagnosed simultaneously with the primary. Most were myocardial metastases at the right heart and occurred in advanced cases at first treatment. A few had reached extensive involvement.

Scharl has reported on a patient (F29) in whom at autopsy metastases were found in the myocard of the right ventricle, but also in the tongue and the kidneys. The rare situation of intracardiac extension from a pelvic intravascular tumor thrombus has been reported in a patient F55 eight months after surgery (Vargas-Barron et al.). Greenwald et al. reported on three cases of cervical cancer with cardiac metastases. Like most of the patients whose data are in table 11.152, they had many other metastases elsewhere.

Table 11.152 - Cancer of the Cervix Uteri
Cardiac Metastases - Literature reports

Author	Pat	Stage	Site	Interval
Heart				
Dibadj 1967	F56	III	Ri.ventricle	11 mo
Ritcher 1979	F32	IIB	Ri.ventricle	8 mo
Thomas 1980	F38	IIB	Le.atrium	3 yrs(')
Itoh 1984	F64	IIA	Ri.ventricle	3 yrs
Hands 1986	F43	IB	Le.ventricle	1 yr
Scharl 1988	F29	II	Re.ventricle+sept	4 mo (')
Kountz 1993	F28	IIB	Ri.ventricle	10 mo
Mohammed '95	F64	IIIB	Ri.atrium+ventr	7 mo
Batchelor '97	F43	IIB	Ri.ventricle	5 mo
Batchelor '97	F51	II	Ri.heart ++	3 yrs
Batchelor '97	F65	?	Ri.heart	2 yrs
Mathlouti '97	F50	II	both atria	3 yrs
Ando 1997	F41	IIB	Ri.ventricle	8 mo
Lemus 1998	F53	IB	Ri.ventricle	18 mo
Lemus 1998	F49	IIIB	Ri.ventricle	6 mo
Senzaki 1999	F28	II	Extensive	10 mo
Sergi 2000	F50	IIA	Both ventricles	7 mo
Harvey 2000	F44	IB	Ri.ventricle	6 mo
Pericard				
Charles 1977	F46	IIIB	Tamponade	1year
Rieke 1988	F49	IIA	Tamponade	6mo
Rudoff 1989	F27	IIIB	Tamponade	11mo
Malviya 1990	F42	IIIB	'Shortness'	type 1
Malviya 1990	F37	IIIB	Cardiomegaly'	simult
Nelson 1993	F51	III	Tamponade	simult
Nelson 1993	F61	III	Tamponade	simult
Jamshed 1996	F57	IB	Tamponade	2years

(') part of widespread metastases.

Table 11.153 - Cancer of the Cervix Uteri
Metastases to the Breast - Literature Reports

Author	Pat	Stage	Site	Interval
Nayar 1987	F35	III	Multiple Bilat	Reveal
Ward 1989	F48	IIB(')	Right large	4 yrs
Singh 1990	F30	IIA	Right	7 mo
Kelley 1991	F32	IB	Left	2 mo
Schumacher '92	F78	III	Le central	17 mo
	F60	IIB	L. UpperOuter	10 yrs
Younathan '92	F48	IIB	Ri.Upper Inn	9 yrs
Kumar 1994	F52	IIB	Right	8 mo
Gupta 1997	F45	IIIB	Bilater.Mult.	1 mo
Kelkar 1997	F51	IIB	Le. Upper Outer	Type 1
Kumar 1999	F34	IIIB	Ri.Up.Outer	5 mo

(') papillary adenocarcinoma

Metastases to the Breast

Several case reports have appeared (table 11.153).
Breast metastases presenting first are rare but misleading. The diagnosis becomes very difficult when the clinical picture is that of a localized lymphangitic inflammatory aspect.

Metastases to the Bone

This also is an uncommon occurrence in cervical cancer. Its incidence rate is between 3 and 15%. Various different pathways to bone metastases can be identiffied in cervical cancer (table 11.154)

Table 11.154 - Cancer of the Uterine Cervix
Pathways of bone metastases

1. Within the pelvis: contiguous invasion
2. At lumbar spine: contiguous invasion from metastatic lymph node (fig.11.35);
3. The pathway of Batson in the pelvis and spine
4. Hematogenous anywhere

Fig. 11.35 - Schematic CT view of metastatic node invading a lumbar vertebra.

The axial skeleton is mainly involved, but precise data are scarce.
Isotope bone survey also have a very low rate of detection, compelled with a high rate of false-positive due to the low specificity of the imaging method.
The great majority are osteolytic, but osteoblastic metastases have been observed.
In 62 patients with bone metastases, or 14% of 1,347 patients, Barmeir found 54% in the spine, 24% in the pelvis, 11% in the long bones and 10 % in ribs, skull and scapula. Compared with other primaries, the incidence in long bone and other was relatively high.
Gilly et al. observed 26 patients with bone metastases in a series of 1,332 patients or 2.0%.
More detailed data were given by Blythe et al. (table 11.155).

Table 11.155 - Cancer of the Uterine Cervix
Metastases to the Bone -Site distribution
Data of Blythe et al.

Spine Cervical	0	Long Bones	
Thoracal	19	Tibia	3
Lumbar	23	Fibula	2
Sacrum	4	Femur	5
Pelvis	17	Humerus	1
Ribs	6	Foot	1
Scapula	1	Skull	1

The authors stressed the fact that several bone metastases in the pelvis and the lumbar region resulted in fact from contiguous invasion by the primary or by metastatic lymph nodes (fig. 11.35).
Similar data were published later in respect of 48 patients by Matsuyama et al. Bone metastases occurred in 70% during the first year of follow-up.
In 1988, Dalicho et al. reported of a woman aged 68 who presented one month after surgery with a 'swollen' little finger, metastatic at amputation. One month

later patient came to autopsy and widespread metastases were found.
A woman aged 72 presented at surgery for a large ulcerated big toe. Radiology showed osteolysis and pathology an epidermoid carcinoma. She was found to have a stage III cervical cancer (Fuchs et al.).
A metastasis to the hip occurring 26 years after surgery in a patient was reported by Maddox et al.

Spinal metastases can be complicated by spinal cord compression. Specific reports for cervical cancer are rare. Ampil et al. have reported on 7 patients. They all concerned epidermoid cancers, stage III or IV at diagnosis. In five the lumbar spine was involved, while in one it was thoracal and in another cervical. Saphner mentioned two cases in their 99 patients with neurological complications from a cervical cancer.

From a series of 121 patients seen within one year, Robinson et al. encountered 5 cases, or 4%, with spinal cord compression. In two, it was present at initial diagnosis. In three it concerned stage IB lesions. A bony or tumorous paraspinal mass was seen at CT with compression of the cord. The level involved was low thoracal in three, cervicodorsal in one and lumbar in the last one. Except for the cervical, the description correspond to an invading tumorous masses from lymph nodes.

The rare site of metastasis to the temporal bone occurred 4 years after first treatment in a woman 44year old. Tinnitus was the first symptom, but final diagnosis was made only at autopsy, 6 months later. She apparently had diffuse and widespread bone metastases (Katsarkas et al.).

Table 11.156 - Cancer of the Uterine Cervix
Metastases to the skin - Literature Reports

Author	Pat	Stage	Site	Interval
Freeman 1982	F69	III	Abdomen (“)	2 mo
Shimizu 1983	F59	IIIB	Scalp	6 mo
Thakaram 1985	F55	IIIB	left thigh	4 yrs
Malfetano 1986	F59	IIIB	Abdomen (“)	2 mo
Malfetano 1986	F41	IIIB	Abdomen (“)	4 mo
Malfetano 1986	F58	IB	Abdomen (“)	4 yrs
Franciolini ‘90	F79	T3N0	Thigh nodule	3 mo
Böhme 1990	F52	II(?)	Scalp	2 mo
Bachaud 1990	F32	IIB	Abdomen(“)	2 yrs
Hayes 1992	F37	IIB	Upper Back	4 yrs
Petit 1995	F36	situ	Infra-clavic.	3 yrs
Ihm 1996	F73	IB	Vulva-Bowen	9 yrs
Pertzbor, 2000	F54	III	Hand - finger	simult.
Umbilicus				
Daw 1982	F43	situ	Umbilicus	10 yrs(°)
Thakaram 1985	F60	IIIB	Umbilicus	3 yrs
Nauman 1995	F41	IIIB	Umbilicus(‘)	5 mo

(“) large cutaneous eruption, lymphangitic type
(‘) after laparoscopy with diffuse intra-abdominal spread
(°) part of widespread metastases in abdomen, liver and spine

Skin Metastases

Cancer of uterine cervix readily metastasizes to the skin. Various different forms have been described, as in other primaries.

Table 11.156 shows that most cutaneous metastases were at the abdomen or thigh, with a clinical picture of lymphangitic spread and a multimicronodular aspect. As most had also intra-pelvic and/or intra-abdominal spread the most likely explanation is a blocked lymphatic reflux.
From a series of 1,190 patients, 15 or 1.3% developed skin metastases within a mean interval of 17 months (Imachi et al.). Multiple lesions were present in 10 patients and were nodular in 13. It was the first sign of recurrence in 9 patients. There were lesions everywhere, but in only 6 was a lesion noted in the upper half.

Other Metastases

We found two reports on cervical carcinoma with H&N metastases. Five years after surgery the patient presented with dysphonia due to a metastatic process in the arythenoid region (Glanz et al.). Another presented with dysphagia one year after first treatment. She was found to have a metastasis in the base of the tongue (Knöbber et al.). A patient (F41) was reported by Barthez et al., as presenting with a small nodule within the left parotid. This turned out to be a metastasis from a cervical cancer, which the patient had neglected to report at first presentation.
One year after the diagnosis of a stage IV cancer, a F49 mentioned left-sided facial pain. It turned out to result from a metastasis involving the middle and posterior ethmoid air cells, the sphenoid sinus and the olfactory recess of the nasal fossae (DeLara et al.).

From the different series of thyroidal metastases reported, only 5 cases of squamous carcinoma of the cervix metastatic to the thyroid could be found, no further details being given and apparently only at autopsy. Recently, Cheung et al. reported on a woman with a long-standing non-toxic goiter, in whom 1 year after treatment, multinodular metastases were found in the thyroid, following progressive enlargement of the goiter. It was complicated with by neck and mediastinal metastatic epidermoid lymph nodes.
Muscle metastases are uncommon in cervical cancer. A patient (F35) with metastasis within the temporal muscle has been reported by Challagalla et al. and another patient with metastasis in the deltoid muscle by Thomsen et al.

While splenic metastases are now currently being reported in endometrial adenocarcinoma, we found only two cases in a patient with cervical cancer. A woman aged 47, presented 4 years after first treatment with a large painful mass in the left hypochonder and no other evolutive site. Laparotomy allowed excision

of a 19 cm splenic mass (Carvalho et al.).
A similar case was reported by Valls et al. Fourteen months after surgery for an adenocarcinoma, CT disclosed a voluminous metastasis in the spleen.

Strange is the absence of reports on renal metastases. DelaTaille et al. described a bilateral revealing metastasis in a patient (F32), first interpreted as abcesses, associated with multiple pulmonary metastases.

Involvement of the placenta was found in a patient aged 36, with a cervical cancer diagnosed a few weeks before delivery. Several metastatic nodules were found in the placenta. The child was apparently healthy, but the patient died a few months later from progression of the disease (Cailliez et al.).

Causes of Death

The majority of deaths from cervical cancers occurs from renal failure due to ureteral obstruction (table 11.157). The resulting uremia and other metabolic disturbances is responsible for an additional number. Other metastatic sites can become more preponderant and result in organ failures such as in the liver and lungs.

Table 11.157 - Cancer of the Uterine Cervix
Cause of Death (N=278)
Data of Badib et al.

Renal failure	30.0%
Infection	10.4
Respiratory failure	10.0
Cardiac failure	4.7
Liver failure	2.5
Hemorrhage	2.5
Central Nervous System	2.2
Other primary	7.5
Other causes	30.2

Overall Lessons

Cancer of the uterine cervix is, like most of the pelvic tumors, a malignancy evolving intrapelvically, with possible extension in the lower abdomen and retroperitoneally. Distant metastases with the exception of hepatic and pulmonary metastases are uncommon, but misleading because of their rarity. When one metastasis is observed clinically, in almost all cases many other ones will be present.

METASTASES from CANCER of the VAGINA

Cancer of the vagina is not a frequent malignancy. This means that large series are not present in the literature and that only a few data are at hand concerning distant metastases.
Like the other pelvic tumors, cancer of the vagina mainly evolves within the pelvis, with contiguous invasion of the neighbouring organs and structures, together with extended lymph node meta-stases.
Invasion by contiguity of the wall of the urinary bladder and rectum is not uncommon.

Lymph Node Metastases

The lymph drainage of the vagina is different for the different thirds. The upper third follows routes like the cervix, the mid portion will follow the perivesical lymphatics to the external iliac chain, while the drainage of the lower third is similar to the vulva and involves the superficial and deep inguinal nodes (fig. 11.36) (Hunter).

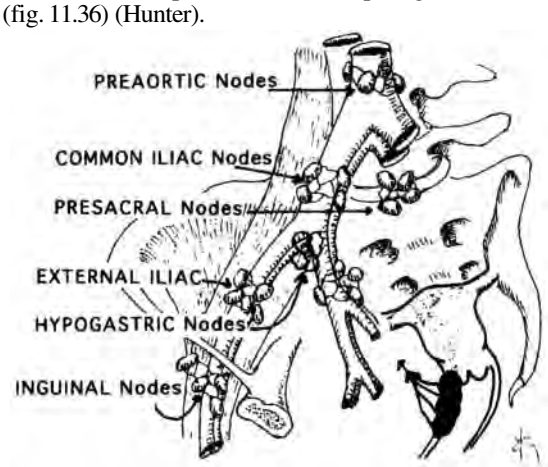

Fig.11.36 - Lymphatic drainage of the vagina within the pelvis.

Some data are found in the review of a relatively large number of cases (table 11.158).

Table 11. 158 - Cancer of the Vagina
Regional and Distant extension (N=37 (‘))
Data of Sheets et al.

Bladder	7	Liver	3
Parametria	4	Brain	1
Rectovaginal sept	4	Lungs	1
Inguin.nodes	3	Ant.Chest wall	1
Abdomen	2		

(‘) clinical series

Distant Metastases

Distant metastases are rare. From a series of 91 patients, 14 developed metastases, 4 of whom had distant metastases at presentation (Houghton et al.). This shows that metastases can also reach the supraclavicular nodes.

Inguinal nodes in	3
Supraclavicular nodes	2
Vertebral bone	4
Hepatic	2
Pulmonary	3

In their review of 70 cases, Dixit et al. reported that distant metastases were found in only three cases, all

at stage III. They were noted in the lung, the pelvis and spinal vertebrae, and were all concomitant with locoregional disease. We did not find any data on the involvement of pelvic nodes at surgery.

A few case reports have appeared on particular metastatic sites.
Two head and neck metastases have been reported, one to the nose by Cohen in 1931 and one to the anterior palate (Carl).
Kouvaris has reported on an extensive nodular dermal lymphangitic spread over the inguinal zone and hypogastrium, most probably caused by lymphatic reflux after intensive radiotherapy.
Bakri et al. have reported on a patient presenting with umbilical discharge six months after radiotherapy. It was apparently merely the top of the 'iceberg' of widespread abdominopelvic dissemination.
Pulmonary lymphangitic carcinoma as first presentation, has been reported by Koenigs. At autopsy widespread pelvic and mediastinal metastases were also found.
Thirty months after first treatment for a vaginal adenocarcinoma, a woman F23 experienced dyspnea and non-productive cough. Bronchoscopy confirmed a extensive endobronchial metastasis, as was suggested by radiology (Millman et al.).

Cardiac metastases developed 4 years later within the right ventricle in a patient treated for a cloagenic (transitional) cancer of the vagina (Ghosh et al.).

An overview of the case reports is in table 11.159.

Table 11.159 - Cancer of the Vagina
Case-Reports on Distant Metastases

Author	Patient	Site of Metastasis	Interval
Cohen 1931		Nose	
Carl 1980		Palate	
Millman 1981	F21	Endobronchial	30 mo
Koenigs 1983	F70	Pulmon.Lymph.	12 yrs
Bakri 1991	F60	Umbilicus	8 mo
Kouvaris 1999	F66	Skin	6 mo
Ghosh 2000	F44	Cardiac	2 yrs
Li 2000	F54	Lungs bilateral	4 yrs

METASTASES from CANCER of the VULVA

Cancer of the vulva can be considered a cancer of the skin, but one with a relatively rich vascular and lymphatic network. This explains its somewhat higher metastatic rate.
There is an extensive literature on vulvar carcinoma as far as diagnosis, treatment modalities and prognos-tic factors are concerned. Distant metastases are proba-bly rare, but hardly discussed.
We found 12 reports on distant metastases, apparently more than for vaginal cancer.

Lymph Node Metastases

The lymphatic drainage (fig. 11.37) follows cutaneous channels toward the inguinal nodes and further toward the pelvic iliac nodes. Infiltration and invasion of the vaginal wall is not uncommon in advanced cases.
Data on lymphatic involvement are scarce.

The frequency of involvement increases with stage (Iversen et al.) (table 11.160). Similar data were reported earlier by Collins et al. with no positive pelvic nodes when the lesion is smaller than 3 cm. Of the pelvic nodes, the obturator was the most frequently involved.

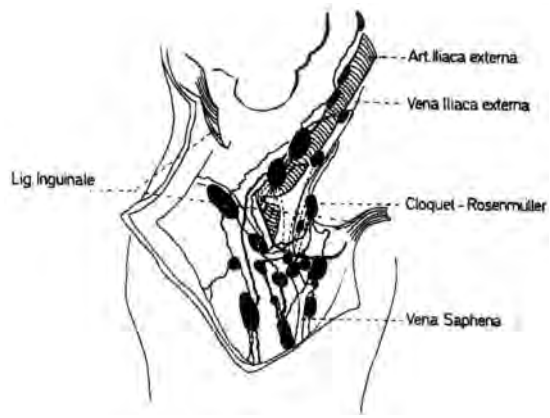

Fig.11.37 - Lymphatic drainage from the vulva

Table 11.160 - Cancer of the Vulva
Lymph node involvement
Data of Iversen et al.

	Inguinal N=262	Pelvic N=100
Stage I	10%	0
Stage II	29%	3.0
Stage III	67%	11.1%
Stage IV	100%	--

Distant Metastases

Thoracal metastases of various types have been reported.
Pulmonary tumor embolism was found at autopsy, 6 months after first treatment, when the patient presented with an acute pulmonary symptomatology. Peritoneal carcinomatosis was also found at autopsy (Soares et al.).
The rare presentation of cavitary pulmonary metastases was seen in a patient treated by radiotherapy. Pleural effusion was mentioned in a patient presenting with a pathological fracture of the femur (Sharma et al.).

Within a month of surgery, a patient aged 70, suffered an attack of unconsciousness. A diagnosis of heart block was made, but a few days later she died. At autopsy, pleural metastases were seen, as wall as one at the apex of the right ventricle, together with several endocardial deposits (Htoo et al.).

Cutaneous metastasis distant from the perineum has been reported in several patients. Like for vaginal carcinoma, its cause can be an intrapelvic lymphatic obstruction. Prignano et al. described multiple abdominal nodular lesions over the abdomen of a women presenting for the first time, but with multiple gross inguinal and pelvic metastatic lymph nodes. The case reported by Tobias et al. with cutaneous metastases at the thigh and the buttock also demonstrates the more segmental spread, compatible with lymph reflux. The status of the pelvic and/or lymphatic lymph channels is never reported in the cases.

Other patients with epidermotropic metastases (Saruk et al.) and with inflammatory type metastases (Cianfrani et al.) have been reported. Metastasis to the scalp from a vulvar epithelioid sarcoma was reported by Weissman et al.
About one month after surgery, a F57 presented with several nodules over the right buttock, confirmed at histology as metastatic from a squamous carcinoma (Tobias et al.).The report on the case described by Saruk et al. would , however, suggest a metastatic recurrence of a uterine cervical tumor.

Table 11.161 - Cancer of the Vulva
Case-reports on Metastases

Author	Pat	Site	Interval
Cardiopulmonary			
Htoo 1973	F70	Ri.Ventricle	
Taryle 1979	F53	Cavitary Lung metastases	
Greenwald 1980	F62	Myocardium	1 mo
Greenwald 1980	F55	Left Ventricle	4 mo
Greenwald 1980	F72	Heart	6 mo
Sharma 1985	F68	Pleural effusion	
Pulmonary Tumor Embol			
Soares 1990	F60	Peritoneal carc	6 mo
Bone			
Seltzer 1976	F59	Ri.Ulna	1 yr
Brufman 1978	F46	Le.Tibia	7 mo
Sharma 1985	F68	Femur	4 mo
Sharma 1985	F49	Femur	6 mo
Sharma 1985	F78	Femur + tibia-fibula and foot	1 mo

Several patients with bone metastases have been reported, without any particular pattern evident, but all in the lower part of the body, mainly in the lower extremities (table 11.161). Abdul-Karim et al. mention 4 cases of skeletal metastases, 2 in the spine and two in the pelvisthough no further data were given.

A metastasis in the left tibia eight months after surgery, has been reported by Brufman et al.
Metastases from vulvar carcinoma are almost certainly underreported. All of the patients whose data are shown in the table reported on table also had, however, many other metastatic sites, but were reported because of the most important clinical feature.

METASTASES from GESTATIONAL TROPHOBLASTIC MALIGNANCIES

Trophoblastic malignancies originate from the placenta and must be differentiated from molas. They are aggressive tumors. A great majority of these can presently, however, been cured by appropriate chemotherapy.
The trophoblast proliferation invades the myometrium and will reach the general circulation by invading its veins.

Trophoblast cells enter the maternal blood stream in every normal pregnancy and are transported to sites such as the lung. Hence both invasiveness and metastatic spread are features of normal trophoblast and an invasive mole is, as are all moles, an abnormal preg-nancy in which the trophoblast is displaying its abnormal characteristics, albeit in an exaggerated degree. The fact that molar trophoblast is transported to extra-uterine sites is thus not an indication of neoplastic behavior (Fox). Incomplete resorption or evacuation of mola will result in persistent gestational trophoblastic disease (pGTD).

Hematogenous metastases occur in 5% of the pGTD following molar pregnancy (table 11.162). They are classified as high risk patients. Invasive or spreading pGTD is then termed gestational choriocarcinoma.

Table 11.162 - Gestational Trophoblastic Disease
Relative Incidence of Metastases

	Berkowitz 1981	Azab 1988 N=162	Hunter 1990 N=134
Lungs	80%	24.7%	93%
Vagina	30	6.8	16
Pelvis	20	2.5	7
Brain	10	3.0	7
Liver	10	1.2	4
Bowel, kidney, spleen each less than 5%			
Other sites, less than 5%			

Although metastatic disease presents initially in the lungs or pelvis, initial clinical symptoms suggesting metastatic disease may masquerade as a cerebrovascular accident, space-occupying lesion in the brain, hyperthyroidism, pneumonia, pulmonary emboli, metastatic lung lesions of an unknown primary, hepatic tumor, breast tumor, gastrointestinal bleeding due to isolated lesions in small or large bowel, hematuria due to involvement of the upper or lower urinary tract, vaginal bleeding due to disease in the vagina or uterus and even unique metastases to the gingiva or skin.
Some specific features of the metastases of trophoblastic disease are
- they may appear as first manifestation,
- they may appear late after any pregnancy,

- they may be related to a previous preg-nancy,
- the rather high incidence of hemorrahagic and acute presentation.

Metastases must be differentiated from the rare primary organ choriocarcinomas. On very rare occasions metastases present during pregnancy and resulting from the previous one.

Thoracic Metastases

The most frequent site of metastases are the lungs, about 80% of patients with metastases. They can occur as:

- discrete rounded densities, one or more coin lesion
- in an alveolar pattern,
- in an embolic pattern,
- a pleural effusion, or a combination of these.

Clinically, they manifest as a progressive dyspnea, pneumonia or unexplained pulmonary hypertension. About half of the patients with lung metastases have more than 10 nodules. The size can be very large: 45 % will have nodules over 5 cm diameter, according to Bakri. They observed pleural effusion in 36 of the 75 with pulmonary involvement, or 48%.
Of 57 nodules observed in 13 patients, only 28% were in the upper third. Hendin notes that this differs from the usual basilar distribution found in lung metastases of other neoplasms. They suggest that this is due to the recumbent position of the patient at curettage of the moles, but this needs a larger patient number to be proven.
Chest CT reveals micrometastases in about 40% of the patients with suspected non-metastatic disease (Berkowitz).
In a number of patients, lung alterations were the first presentation sign of the disease.
Spontaneous pneumothorax due to metastatic disease is rare. One case has been reported by Ouelette et al. and one by Santhosh, where the pneumothorax was the presentation sign of an unknown metastatic choriocarcinoma.
A peculiar endoarterial pulmonary metastasis has been reported in a patient with term intrauterine pregnancy, without any visible tumor anywhere else (Carlson et al.).
A 33-year-old woman presented with recent progredient dyspnea with signs of pulmonary hypertension. Her last delivery was 10 years previously, followed in the meantime by three abortions. Pulmonary arterial wedge biopsy disclosed maligant cells and hCG turned out to be very high, confirming multiple recurrent tumor emboli from a trophoblastic malignancy (Bhuvaneswaran et al.).

A 38-year-old woman presented at Emergency with right-sided pleuritic pain and hemothorax. She died a few days later from an acute abdomen. At autopsy, a ruptured adnexal mass and multiple nodular pulmonary metastases were found with the histology diagnosis of choriocarcinoma. Fifteen months before she had an 'abortion' and four months previously ametrorrhagia that was not investigated further (Wolkove et al.).

Not every lung pathology detected at CT is a metastasis. A formerly present benign lesion can render the final diagnosis difficult. This is very well demonstrated in the report by Kohorn, who reported on two patients where histology of the surgically resected mass disclosed a benign hamartoma or a benign teratoma.

Metastases to the Brain

Brain metastases have the clinical signs of an expanding lesion or/and hemorrhage intracerebral, subarachnoidally or subdurally. Patients may present with an acute stroke or an encephalitic syndrome. Intracranial hemorrhage is the presenting mode in 66% and may be subdural, subarachnoidal or intracerebral (Pullar et al.). In several series, there is a predominance of the left frontal lobe. The cerebellum is a rare metastatic site, occurring in less than 10% of cases.
The clinical picture of brain metastases is very variable (Adeloye). More detailed data on site (table 11.163) and the clinical manifestations (table 11.164) were provided by Yordan et al. A serum/CSF β-HCG ratio value less than 60 was reported as facilitating early diagnosis, but this has not been confirmed (Bakri et al.).

Table 11.163 - Choriocarcinoma
Brain metastases - Involved site (N=47)
Data of Yordan et al.

Frontal Lobe	43%		
Temporal	15%	Spinal	9%
Parietal	45%		
Occipital	23%	Left 68%-Right	32%
Cerebellum	9%	Unifocal	79%
Brain stem	4%	Mulifocal	21%

Table 11.164 - Choriocarcinoma - Brain metastases
Clinical manifestations (N=66)
Data of Yordan et al.

Headache	55%	Paresthesias	5
Paresis	49	Syncope	5
Cranial nerve inv.	36	Amnesia	5
Decreased Sensorium	29	Incontinence	5
Seizures	24	Hyperthermia	3
Nausea-Vomitus	23	Abnorm.Reflexes	2
Aphasia	17	Photophobia	2
Meningism	8	Tinnitus	2
Papilledema	8		
Behavioral Changes	6	Asymptomatic	8

The secondary oncotic intracranial aneurysmal form is a very unusual form of brain metastasis. The few cases (11 up to 1987) were all localized within the branches of the middle cerebral artery. This is an unusual but also highly lethal complication of choriocarcinoma (Seigle et al.). The spectrum of vas-

cular damage can be explained in terms of several mechanisms proposed by Pullar et al. Aneurysm formation, destruction of the vascular wall, involvement of multiple adjacent vessels and secondary cerebral infarction or a combination can be involved.
The incidence of neoplastic aneurysm is probably higher than reported in the literature.

Not every brain pathology detected at CT or MRI is a metastasis. As always, a second tumor can be present. This is very well demonstrated in the report by Kohorn, who reported on a patient where CT-MRI disclosed a cerebellar hemangioma.

Metastases to the Liver

Liver metastases also present as pain (Glisson-pain) or even hemorrhage within the abdominal cavity. Its incidence at presentation is between 1 and 10%, 2.7% in the series of Crawford et al.
The liver metastases can be single, but in most cases they are multiple. About 80 to 90% of patients have lung metastases, and when brain metastases are also present (60%), there are likely to also be pulmonary metastases.

Several case reports concern acute abdomen due to hemorrhagic peritoneum. An acute abdomen in a postpartum, but also several months or years after a normal partus, must rise the suspicion of an unknown gestational choriocarcinoma (table 11.165).

Table 11.165 - Choriocarcinoma
Acute Liver Hemorrhage Reported

Author	Pat.	Pregnancy	Interval
Grumbine 1980	F25	Hydat.mole	10 mo
Heaton 1986	F29	Normal	8 yrs
Heaton 1986	F27	Normal	7 yrs
Alveyn 1988	F34	Normal	2 yrs
Erb 1989	F29	Normal	1 mo
Roumilhac '99	F23	Normal	2 mo

The incidence of hemorrhagic metastases is about 10% of the 46 patients with hepatic metastases in the series of Crawford et al.

Metastases to the Head and Neck

Rare metastases have also been described within the choroid, thyroid, the tonsil, the nose, the skin, the breast, the kidney, a finger (first symptom), the spleen, the maxillofacial region and the fetus (case reports on table 11.166). To our knowledge, only 2 cases of choroidal metastases have been reported in the lite-rature. One case manifested itself 4 years after pregnancy, while no further details are known about the other case (Barondes et al.). Almost all patients had several other simultaneous, mainly pulmonary metastases.

Table 11.166 - Choriocarcinoma
Metastases to the Head and Neck - Case Reports

Author	Pat.	Pregnancy	Site	Interv
Marikar 1959	F20	ChorioCa	Nose tip	6 mo
Betson 1962	F23	Mola Hyd.	Nasophar.	1 yr
Ramanathan '68	F22	ChorioCa	Palate-Maxill	1 yr
Kutty 1971	F40	Mole	Ri.Tonsil	4 yrs
Bakeen 1976	F25	Chorioca	Gingiva	simult
Salmi 1977	F35	Mola Hyd	Nasal cav	12 mo
Sato 1978	F32	Mola Hyd	Gingiva	6 yrs
Mukherjee 1975			Nose	
Sesenna '85	F19	Mola	Mandible(*)	4 yrs
Tharakaram '86	F27	Abortion(°)	Nose	8 mo
Barondes '89	F32	Normal	Choroid	4 yrs
Conlon 1991	F33	Normal	Choroid	5yrs(")
Erdogan 1994	F34	Normal	Thyroid	4 yrs
Ganadharan '99	F27	Mole	Orbit(')	14 mo

(°) curetage disclosed CC
(') in F.U., after treatment for other metastases
(*) in processus coronoideus
(") choriocarcinoma is not well outlined in the report

The patient reported by Marikar et al. developed several skin metastases, among which the typical 'clown-nose' and other lesions over the scalp and the shoulder.

Metastases to the Kidney

Probably occurring in a number of patients, many are brought to the attention by acute perirenal hemorrhagic situations or hematuria. In autopsy series, renal involvement varies from 10 to 50%. Soper et al. mention an incidence of less than 2% in the primary referred patients, but in 14% in those referred for secondary treatment. The renal symptomatology is part of a clinical picture characterized by many other pulmonary and abdominal metastases.
At arteriography, the choriocarcinoma metastases present as intensely vascular lesions with arteriovenous shunting (Kutcher et al.). A few cases with perinephritic extracapsular fluid collection due to hemorrhagic metastases disclosed at CT have been reported (Mastrodomenico et al.).

Other Metastases

Metastases in the vagina (up to 30%) will mainly be in the fornices or peri- or suburethrally. Hemorrhage is the symptom, as it is for localisation in the bladder or the kidney. About 10% of them have liver and/or brain metastases.

We are aware of two reports on metastases in the breast. The two reported and the two retrieved from the literature in a review all had at least lung metastases (Alvarez et al.).

Noteworthy in one case was that several skin metastases appeared in the gluteal region. In all of them it was part of extensive metastases (Ertungelap). (See also above, the case of Marikar et al.).

Hetzel et al. have reported on a woman presenting one month after a normal delivery with a large metastasis in the distal left fifth finger, which turned out to be the presenting sign of widespread gestational trophoblastic disease.
Three years after evacuation of a HM, a F40 presnted with a subungual metastases (Seoud et al.).

An extramedullary located tumor compressing the spinal cord was excised two years after hysterectomy for 'uterine' choriocarcinoma in a F44 (Veskonakli et al.). Kuten et al. had reported a smilar case earlier as well as Beskonakli et al.). Bone metastases are rare, with one probable case reported (Vani et al.).

Perroni et al. have reported on a case with metastases in the right heart ventricle. They found 4 cases in the literature up to 1993 and also a case with coronary tumor embolism. A metastasis within the left ventricle, probably secondary to the multiple lung metastases, was reported by Seigle et al. The patient had aneurysmal hematomas in the brain and at autopsy metastases were also found in the spleen, the gastrointestinal tract, the kidneys and the brain.
A dramatic case involved a young woman presenting 1 year after delivery with dyspnea and tachypnea. Six months previously, she had received chemotherapy for uterine choriocarcinoma. At ECG and other investigations, it was considered ischemic heart disease. At autopsy however, subepicardial coronary vessels and intramyocardial arteries were found to be completely occluded by metastatic choriocarcinoma (Vasiljevic et al.).

Metastases to the Fetus

Another rare presentation is that of multiple visceral lesions appearing in the newborn from a gestationally derived placental metastasis or neoplasm, so-called 'infantile' choriocarcinoma. It manifests in the first weeks or months while the mother remains apparently free. In all cases, disease 'appeared' in the mother within the next months. (Kalifa et al., review by Belchis).
The syndrome was first described by Witzleben et al. involving a constellation of clinical and laboratory findings consisting of anemia and/or pallor and hepatomegaly. We found 21 cases in the literature (table 11.167). In about one quarter, the symptoms are manifested at birth and in most of the fetuses, autopsy disclosed multiple metastatic sites, mainly liver, lung and subcutaneous nodules. In their timely review, Belchis et al. added two other less frequent types of presentation. The first is a intra-uterine fetal demise with hydrops fetalis and the other present with massive feto-maternal hemorrhages.

Table 11.167 - Infantile Choriocarcinoma, with or without Maternal Involvement

Author	G	Age	Symptoms	Involvement	Mother
Emery 1952	M	36 wks	Blood vomiting	Lung Liver	None
Kay 1952	F	7 wks	Blood sputum-Hematuria	Lung Liver	None
Butchell 1954	M	7 wks	Vomiting Pallor Abdominal Distention	Liver	CC
Mercer 1958	??	3 mo	Recurr.Hemorrhagic Nodule gingiva	Alveolar Ridge	CC
Daamen 1961	??	6.5 mo	Pallor	Hemoperitoneum	CC
Wizleben 1968	??	5 wks	Hematuria - Melena Hemoptoe	Liver-Lung Brain	CC
Kelly 1971	??	birth	Pallor - Lethargy	Brain Liver Lung	No residual
Blackburn 1976	M	birth	Pallor - Tachypnea	no follow-up data	CC
Feldman 1977	M	birth	Pallor	NOD 4mo	CC
Brewer 1981	??	36 wks	Bleeding	Lung Vagina	None
Brewer 1981	??	18 wks	Vaginal bleeding Fever Dyspnea	Lung Vagina	CC
Brewer 1981	??	30 wks	Headache Convulsion	Liver Brain	CC
Brewer 1981	??	32 wks	Headache Paresthesia	Lung Brain	CC
Nieuwenhuys 1977	F	0	Fetal death	Kidney	CC
Kalifa 1981	M	2 mo	Scalp skin nodules Hepatomegaly	Liver Lung Brain	CC
Aozosa 1981	F	2 mo	??	??	??
Tsukmoto 1986	M	0	Stillborn	Liver Lung Scalp Diaphragm	Parametrial
Avril 1986	F	0	Skin nodules	Lung Skull	None
Flam 1989	F	1 mo	Anemia	Liver	CC
Chandra 1990	M	2 wks	Seizure Icterus	Brain	CC
Belchis 1993	M	2 wks	Vomiting Anemia Liver Melaena Hepatomegaly		None
Dautenhahn 1993	F	3 mo	Pallor Hepatomegaly	Liver Lung Axilla	no data
Picton 1995	M	3 wks	Fetal distress Seizure	Liver Lung Rib	CC

METASTASES from PLACENTAL SITE TROPHOBLASTIC TUMOR

Placental site trophoblastic tumor (PSTT) is a rare form of gestational trophoblastic disease. The low number of cases reported does not allow an adequate estimation of its malignancy, but it seems rather high.

Chang et al. found up to 1999 27 metastatic cases reported. When compared with the non-metastatic cases (table 11.168) the higher age at presentation, a longer interval after the antecedent pregnancy and a higher incidence of term delivery are obvious. The different metastatic sites are listed in table 11.169 showing the preponderance of lung involvement and the high variability of the organs involved.

Table 11.168 - Placental Site Trophoblastic Tumors
Features of Metastatic and Non-metastatic cases
Literature review by Chang et al. 1999

	NonMetast. N = 61	Metast. N = 27
Mean Age (range)	30.0 (19-52)	33.1 (21-53
Serum hCG mean	467.3 (1.1-5129)	1670 (15-8300)
Antecedent pregnancy		
Term delivery	57%	82%
Molar pregnancy	13%	9%
Spont.abortion	11%	9%
Other	19%	

Table 11.169 - Placental Site Trophoblastic Tumors
56 Metastatic sites in 27 cases
Literature review by Chang et al. 1999

Lung	19 (34%)	Pancreas	3
Vagina	8	Bladder	2
Lymph Node	6	Colon	1
Brain	4	Spleen	1
Liver	4	Stomach	1
Ovary	3	Urethra	1
Kidney	3		

(16 patients had more than one metastases)

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Caution: References are given for documentary purposes. Not all have been reviewed or used in the redaction of the text. We do not claim completeness of data. The references are as much as possible grouped per subject heading. For some headings, only reports after 1979 are listed.

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12
METASTASES from TUMORS of the CENTRAL NERVOUS SYSTEM

Tumors of the nervous system, enclosed within its parenchyma, several membranes and the skull, protected by a blood brain barrier, will remain almost lifelong within the craniospinal cavity.
The tumors, however, have some invasiveness as the observed progressive resultant destruction of the neighbouring structures confirms.

As for all tumors, local, regional and distant spread can be identified. The latter has long been thoughtnot to occur, but has been observed in recent decades, althoughonly on rare occasions.

Local Invasion and Spread

Brain tumors, like all malignant tumors, invade along anatomical histological structures. The periphery of the tumor is should be considered the invading front with an undefined border made up of infiltrating cells, local nervous tissue and the reacting glial cells. The cells can form large extensions into the surrounding brain tissue, which becomes edematous. The cells proceed along the nerve fibre tracts into and within the sub-arachnoid spaces and around the blood vessels, forming a circular 'cuff' due to a gradient of nutrient factors.
Glioma cells will also advance within the pia mater and sometimes within the perivascular spaces. From there, they can invade the cortex of the opposite cerebral convolution.
Cells can migrate between pial and arachnoidal spaces along the blood vessels. Common to all gliomas and independent of tumor grade, extensive glioma cell accumulation can be seen along the leptomeninges.

The following step is the transport of cells via the cerebrospinal fluid, after they have entered the subarachnoidal spaces or/and the ventricles, to distant sites within the central nervous system. It will be obvious that as the cerebrospinal fluid has a turnover of 0.5 liter/day, transport of malignant cells will be rapid (Laerum).

Histology and Spread

Differences in spread between the different histology types have been observed (Laerum).

Astrocytomas may present as a diffuse proliferation of astrocytes, spread over a wide area, or localized as clusters around nerve cells under the ependymal lining of the ventricles and in the perivascular spaces of the parenchyma. They often show a diffuse spread into the white matter and tend to make small and large cysts. The cells may invade fibre tracts of the corpus callosum, pons or spinal cord in the form of elongated bipolar piloid shaped cells.
Glioblastomas present with necrosis and hemorrhages, probably because of rapid growth, and extensive spread in the tumor periphery. Within the white matter, the cells infiltrate far outside the area of visible tumor and the adjacent edematous zone and commonly along the nerve fibres. The infiltration is accompanied by extensive destruction of normal tissue though sometimes the extension passes through, leaving some areas intact. Subarachnoidal dissemination is common.
Medulloblastomas are usually well demarcated but rapidly infiltrate the ventricles and grow within the ventricle cavity. The cells infiltrate the brain parenchyme, mainly the cerebellum and invade the leptomeninges with frequent spread into the subarachnoidal space.
The well-demarcated oligodendroglioma tend to spread within the white and the gray matter with subpial and perineuronal growth. Ependymoma behave similarly.

In general, it seems that narrow structures such as the leptomeninges and the vessels behave as non-permissive structures for the further spread.

Patterns of Spread

As can be deduced from the previous discussion, three patterns of spread have be observed for tumors of the central nervous system (Table 12.1, fig.12.1).
The most common is leptomeningeal dissemi-nation, occurring in about 30%, at least in children (Dropcho et al.). Some patients only have microscopic invasion, but multinodular seedling is not uncommon. While this pattern of recurrence may be as frequent as that of a surgically treated tumor, it may be the first presentation of an unknown intracranial primary.

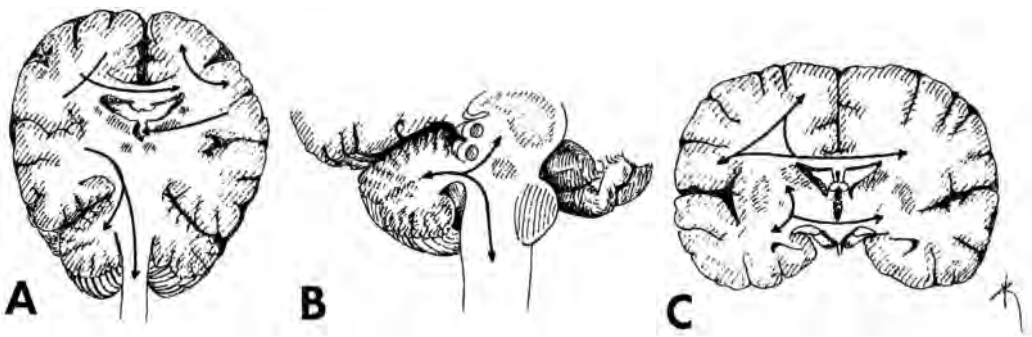

Fig.12.1 - Diagramatic representation of intracerebral spread of primary CNS tumors. (A) In the coronal plane towards the anterior, posterior and heterolateral structures; (B) From or towards the cerebellum to or from the brain or the spinal cord; (C) in the frontal plane within the same hemisphere or to the heterolateral hemisphere.

Table 12.1 -Tumors of the Central Nervous System
Patterns of Spread

Local invasion
Spread within the structures of the CNS
intracerebral
towards opposite hemisphere (corpus callosum)
towards anterior structures (brain stem - cerebellum)
towards lower structures
towards the spinal cord: intramedullary
Intradural seeding
Leptomeningeal dissemination
Extraneural, after perforation of dura mater

Distant microscopic infiltration within the brain parenchyma is observed at autopsy in about 80% of cases.

Astrocytomas have long been known to disseminate intra-axially through the corpus callosum and along fiber pathways towards the brainstem and cerebellum. When originating in the thalamic region, horizontal spread to the optic apparatus and contralateral thalamus is observed, followed by vertical spread in brain stem and cerebellum. This has also been observed in glioblastoma multiforme. Similarly, infratentorial tumors can extend towards the supra-tentorial structures.

Likewise, this spreading modality is probably the origin of intramedullary - within the spinal cord - metastases of the tumors of the central nervous system. Furthermore, it is common for primary spinal tumors to extend in both cranial and caudal directions. Some data on the local spread of cerebral tumors (glioblastoma multiforme) have been reported by Salazar et al. (Table 12.2).

Direct contiguous invasion occurs in 75% of the supra-tentorial tumors. Of the laterally located tumors 60% spread in an anterio-posterior direction. Most tumors involve a second lobe, some even the whole hemisphere.
Spread in a vertical direction to deep supratentorial or intratentorial structures is seen in 20% of the peripherally situated tumors, while those centrally located almost always invade adjacent structures extensively. The corpus callosum and the area of the thalamus are favorite areas for making the passage across towards the opposite hemisphere. This is seen in one quarter of supratentorial tumors. Extensive penetration is observed in all directions for infratentorial tumors.

Table 12. 2- Tumors of the Central Nervous System
Glioblastoma Multiforme
Patterns of intracerebral spread
Data of Salazar et al.

Supratentorial - Peripheral Tumors (N=29)	
Extension within same hemisphere	59%
Extension to central areas in same h.	14%
Crossing to opposite hemisphere	21%
Extension to infratentoral structures	7%
Supratentorial - Central Tumors (N=6)	
Extension to periphery within same h.	2/6
Crossing to opposite hemisphere	3/6
Extension to infratentoral structures	2/6
Infratentorial (N=6)	
Extension to adjacent fossa	5/6
Extension to supratentorial struct.	4/6
Direct extension to spinal cord	1/6

Autopsy was performed in 25 patients with glioblastoma multiforme by Erlich et al. Eight patients showed metastases to distant intracranial sites. In five of 20 patients the spinal cord was found to contain spinal leptomeningeal metastases. This seems to be a common occurrence. They retrieved 14 other cases from the literature (1978). A case with cauda equina involvement and bone metastases (vertebrae and ribs) has been reported by Lampl et al.
The symptomatology of tumor spread depends on the structure invaded and will not be discussed further here.

Extraneural metastases are possible when the tumor cells have gained access to the extrameningeal tissues. This happens spontaneously but most frequently after surgical disruption of the dura mater.

Intramedullary Metastases

First a linguistic note. Stedman's dictionary clearly states that 'spinal' means 'relative to the vertebrae'. Many authors indeed use, however, the word 'spinal' to indicate intramedullary or even intrarachidial processes, evt.metastases. This will lead some inconsistencies, especially when librarians will encode the publications.

Intramedullary metastases from intracranial primary tumors are rare. The mechanisms discussed have led to several speculative theories, but spread along the nerve fiber tracts is certainly possible. In the descriptions of different cases, we have noted the presence of syrinxes in the same 'tract' most frequently above the lesion, and descriptions of elongated tumoral cells, due to deformation during their voyage along the fibers. We are not aware of pertinent experimental studies done, with colored or other substances.

Intramedullary metastases, within the spinal cord, from primary cerebral tumors have rarely been reported. Before the CT and even the MRI era, the diagnosis was rather difficult. Nevertheless, one would have expected more recent reportso n this extension, at least for non-medulloblastoma patients (Table 12.3).

Table 12. 3 - Tumors of the Central Nervous System
Non-Medulloblastoma
Intra-Medullary Metastases Reported

Author	Pat.	Primary	Histol.	Interv	Site
Steimle 1974	F21	Te.Pa Ri.	Gliobl	6 mo	D9-L1
Kepes 1976	F3	Stem	Astroc	4 mo	several
Kepes 1976	M32	Stem	Astroc	18 mo	T11+S1
Tanghetti '83	M52	'Cerebral'	Gliobl	14 mo	T11-12
Onda 1986	M48	Temp.Ri	Gliobl	2 yrs	C5-C7
VanVelthoven'88	F13	Pari.Ri	Oligo	8 mo	T6-T8
Knüpffer 1989	M41	Front.Ri	Gliob	n.d.	Tc-CE(')
Vertosick '90	M18	Pari.Ri	Gliobl	9 mo	cervic.
Vertosick '90	F43	Te.PaRi.	Gliobl	15 mo	midthor
Natelson '92	M42	Front.Ri.	Oligo	15 yr	Occ+
Hamilton '93	M70	Frontal	Gliobl	10 mo	T10
Woesler 1997	F42	Frontal	Astroc	11 mo	cervic.
Setty 1997	M4mo	Suprasell	Astroc	simul	T4
Materlik '98	M33	Frontal	Gliob	20 mo	C7-T1

(') whole thoracic cord and cauda equina

Intramedullary spread from medulloblastoma is more frequent. It is possible that the anatomic location within the cerebellum and/or the ventricles favours this type of spread. While previously noted in selected clinical cases whose 'slow' evolution allowed its diagnosis and surgery, it can now readily be detected with CT and to an even greater extent with MRI.
One of the first cases was reported by Zumpano. It was located around C5, and was clearly without any extramedullary seeding nor other tumoral spread. A few other cases have followed, highlighting the possibilities of MRI.
From a series of 66 patients, Sure et al. noted an unfavorable evolution in 35 or 53%. Several 'secondary' or metastatic manifestations were observed (Table 12.4). Metastases within the cervical cord were noted in 10 patients, or 28% of the group, or 15% of all treated patients.
The latency of the secondary manifestation ranged from 0 to 24 months. The total incidence of 15% justifies a pre-surgical screening.

Table 12. 4 - Medulloblastoma
Pattern of secondary diseases - metastases (N=35)(°)
Data of Sure et al.

Metastases in the Posterior Fossa	2 or 5.7%
Supra-Tentorial Metastases	8 or 22.8%
Diffuse Leptomeningeal	6 or 17.1%
Intramedullary Metastases (')	10 or 28.5%
Extra-axial metastases	8 or 22.8%

(°) 17 patients had local recurrence
(') labeled spinal metastases, but in the text ,clearly stated within the spinal cord.

Some authors have suggested that intramedullary spread arises from invading subarachnoidal de-posits, but authors such as Hamilton and others have failed to detect such evidence on MRI. Others have suggested hematogenous spread, but this is improbable as no other distant metastases have been detected in these patients.
The presence of normal tissue completely surrounding the metastases makes any supposition difficult except the peri-fibre or peri-tract spread from the brain stem on towards the lower segments of the cord, as suggested by the observations of Laerum and of Salazar as discussed above. This would then be analogous to the perineural spread observed in many other tumors (Chapter 7).

Intra-Dural - Leptomeningeal Spread

Intradural spread can be observed as one or many more small or large tumors within the space, or as a microscopic leptomeningeal metastasis. Many times the presentation is a combined one.

Weiss has formerly proposed criteria for the diagnosis of 'spinal' metastases:

1. an histologically proven single brain tumor;
2. the initial symptoms are clinically indicated from the cerebral tumor;
3. autopsy has excluded another malignancy;
4. morphologies of brain and 'cord' tumor are identical.

These criteria were established before the CT and the MRI era and are not always fulfilled in the case-reports, mainly as autopsy is not always permitted.

The clinical presentation, at least of symptomatic patients, is characterized by neurologic deficits, either spinal or cranial nerve palsy, mainly of nervus III: motor weakness, segmental numbness and pain with or without sphincter problems. This will lead invariably to paraplegia.

In the symptomatic group, the mean interval between diagnosis and dissemination is 8 weeks (range 4-240 weeks), probably the presentation of an aggressive tumor group. In the asymptomatic group, where detection will be made by screening-CT, the interval is longer (mean 133 weeks (2 years), range 4-416 weeks) (Arita et al.).

Indeed previously, the extent of tumor seeding could only be appreciated at autopsy. The availability and progressive improvements in imaging methods have allowed it to be delineated in vivo, ameliorating the outcomes for these patients. Illustrative is the report of Moore et al. on 4 patients in 1963. The diagnosis of glioblastoma was made in vivo in two, but in all, the extent of leptomeningeal spread was only discovered at autopsy.

In the articles reviewing intra-rachidial spread, the difference between intra- and extramedullary involvement is not always made. The review by Schwaninger et al. on 23 cases includes a number of cases that were clearly described as intramedullary.

Performing myelography in all of the 34 patients with medulloblastoma, Stanley et al. noted an abnormal myelogram in 15 or 44%. While abnormalities were encountered at all levels, every patient had involvement in the lumbosacral canal.
The features observed were

nodules within the terminal sac	5
nerve root thickening	4
nerve root nodularity	10
obliteration of nerve root sheath	5
diffuse arachnoidal infiltration	2
nodularity or cloaking of the conus	8
mass with myelographic block	1
nodularity of thoracic cord	8
nodularity at cervical cord	3
diffuse leptomeningeal irregularity	1
generalized symmetrical enlargement	2

Acute meningeal symptoms in glioblastoma has rarely been reported. We found only a report dating back to 1976 by Bernat et al., reporting one case and mentioning 8 other ones in the previous literature. Remarkable is that in 5 of them, the glioblastoma was originally located at the corpus callosum. This site has anatomically a certain propensity for CSF dissemination.

The variety in the patterns of intra-rachidial spread can be explained at least partially in terms of the circulation of cerebrospinal fluid. The involvement of the lum-bosacral canal in every patient reflects in fact the effect of gravity upon fluid-born metastases.

In the thoracic region, nodularity and cloaking of the cord is seen with diffuse arachnoidal irregularity, more prominent on the dorsal surface. The caudal flow of the CSF is predominently dorsal with a ventral return, allowing 'incoming' cells to settle first in the dorsal region. The dorsal arachnoidal veils may also act as pocket arrest for the cells within the fluid (fig. 12.2).

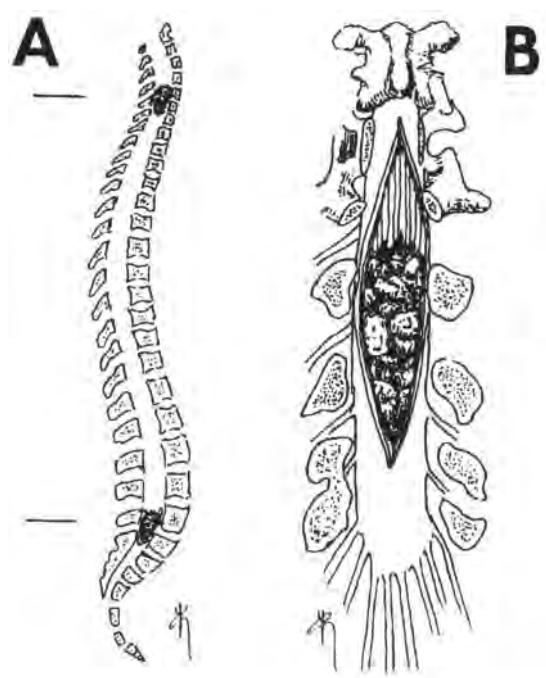

Fig.12.2 - The most frequent sites of intradural seedling over the spinal cord. (A) at the cervical and the lumbar lordosis; (B) at the cauda equina

In the lumbar region one encounters more small discrete noduli or subtle nerve root thickening or large masses causing myelographic blocks.

Table 12.5 - Malignant Tumors of the Brain Ventricular and Spinal Metastases (N=96) Data of Bryan (1974)

Histology	Macro(')	Micro(")	Total	Percent
Astrocytoma IV	29	28	57	59.5%
Astrocytoma III	2	0	2	2.1
Ependymoma IV	7	8	15	15.6
Medulloblastoma	5	4	9	9.4
Pinealoma	3	3	6	6.3
Choroid Plexus	1	2	3	3.1
Oligoastrocyt IV	1	0	1	
Oligoastrocyt III	1	0	1	
Pituitary	1	0	1	
Anaplastic Carcin.	1	0	1	
TOTAL	51	45	96	100%

(') visible nodules; (") microscopic implants

Without stating the total numbers of patients treated for a CNS-malignancy, Bryan reported in 1974 on 96 patients from a single institution over a period of 20 years, all with intraventricular or 'spinal' seeding. Those cases (N=?) with seedlings confined to the external surface of the brain were omitted. More than half concerned astrocytoma grade 4 (Table 12.5). The sites of involvement within the CNS are on Table

12.6. All patients had leptomeningeal spread either macroscopic or at the microscopic level, but site distribution was not reported. Remark that the same proportion is observed between macro- and microscopic involvement, the latter being probably the early stage of involvement.

Table 12.6 - Malignant Tumors of the Brain
Ventricular and Spinal Seeding (N=96)
Data of Bryan (1974)

Observed Site of Implants in the Ventricular System	
Lateral Ventricles alone	20%
Fourth Ventricle alone	18
Both Lateral and Fourth	34
Aqueduct	12
Third Ventricle	4
All sites	12

Previously, Balhuizen et al. reported on CSF cytology in disseminated brain tumors. Of 131 patients, a positive cytology was obtained in 20 or 15.3%, the highest positivity being obtained in cases of ependymoma and astrocytoma grade III-IV (18%). This is substantially less than in leptomeningeal metastases from extra-neural tumors.

Incidental data on leptomeningeal spread in children from one institution were provided by Packer et al. (table 12.7).

Table 12. 7 - Tumors of the Central Nervous System
Incidence of Leptomeningeal Spread in Children
Data of Packer et al. N=254

Tumor-Type	N	With LM	At diagnosis
PNET fossa post(')	61	31 (51%)	18 (30%)
PNET cortex	6	2 (33%)	1
Ependymoma	24	5 (21%)	1
Glioma	94	13 (14%)	4
Glioma cerebellum	36	0 --	
Glioma brain stem	12	1 (8%)	
Germinoma	12	2 (16%)	
Craniopharyngioma	26	0 --	
Other	34	6	

(') Primitive NeuroEctodermal Tumors, including medulloblastoma

The highest incidence is observed in medulloblastoma, in about half already at presentation.
It is also observed, as was suggested previously by other authors, that the patients with LM-spread are younger than those without, 5 yrs vs. 8 yrs at $p<0.02$. When only PNET is considered, the difference is even more pronounced: 4.5 yrs vs.8.0 yrs.

Of 70 aggressively treated supratentorial gliomas, evidence of leptomeningeal spread was observed in 13, confirmed at autopsy, resulting in an incidence of 18% (Awad et al.). High variability in the CT features obtained ante-mortem was noted. Ventriculomegaly, peri-ventricular enhancement and multifocal tumor involvement were the most frequently noted features. Cytological evidence in the CSF was obtained in less than half of the patients, a proportion already observed by Bryan (cfr.supra).

Reviewing 14 cases of glioblastoma with LM spread certified at autopsy, Onda et al. remarked two different patterns. The first group concerned patients with relatively limited tumor extent, though all with extent to the lateral ventricle, while in the other group, most showed extensive infiltration or extensive spread towards the opposed cerebral hemisphere or caudal extension to the brain stem. Ventricular and leptomeningeal seeding was relatively slight and clinically not obvious.

The various case-reports show that most of the tumors, where an important spread occurred, were located very near the ventricles, as far as can be judged from written reports. The second case by Buhl. for example had a large tumor within the temporo-parietal region very close to the ventricles. We also have the impression that several of supra-tentorial tumors leading to LM spread are located in that region, but the literature reports do not allow further evidence to be found, as the data are incomplete, and the total number of tumors situated at that site not reported.
Grabb et al. also observed that almost all disseminating tumors abutted the ventricular surface. Certain locations are more prone to dissemination, particularly the posterior fossa neoplasms.
Based on the study of 26 patients who had died of neuroecto-dermal tumors, Nishio et al. found dissemination in 20 patients or 77%. The apparent predisposing factors are summarized in Table 12.8.

Table 12. 8 - Tumors of the Central Nervous System
Predisposing Factors for Intraneural Spread
Free from Nishio et al.

1. Extension of tumor to ventricular surfaces and CSF
2. The malignancy of the several histologic forms
3. The survival of malignant cells in CSF

Reviewing the literature in 1995, Aghakhani et al. found that for glioblastoma, the frequency of LM spread varied between 13 and 25%, for the supra-tentorial 6% and for the infratentorial 60%. After surgery the amount reaches 40%.

The most frequently involved sites are the brain stem with involvement of cranial nerves, the dorsal part of the thoracic cord and lumbar cord, and the cauda equina, in descending order.

Symptomatology

It is important to know is that only 30% are symptomatic.
Symptomatology in this series of patients may be grouped into four presentations: back pain, spinal cord compression, cauda equina syndrome or hydrocephalus.
The interval between first treatment and diagnosis of

LM ranges from 2 months to 5 years, with a mean of 14 months. The mean age of the patients is relatively young, about 38 years.
In general, this means that patients with glioblastoma should be regularly evaluated with MRI over the whole length of the spinal canal.
One should also remember that in these cases, cerebrospinal fluid cytology has a high incidence of false-negative results and a negative result is non-conclusive for this pathology. Many authors have observed this low rate of positivity.

From the files of the AFIP[1], Pzeshkpour was able to find 18 cases where the intra-rachidial spread resulted in first symptoms before the diagnosis of the intracerebral primary. Of more than 18.000 primary CNS tumors, this would represent an incidence of less than 0.01%. The majority, 11 or 61% were medulloblastoma, and there were 3 glioblastomas, 2 astrocytoma and 1 germinoma. Remarkable is that two-thirds of the patients were male. Age ranged from 3 to 63 years of age, with a mean of 20 years.

ExtraNeural Spread

Long regarded as never occurring, several case reports demonstrating extra-neural distant metastases have appeared. It is certain that the longer life-expectancy due to better first treatment methods has resulted in the higher probability of the emergence of metastases. Nevertheless, in spite of the many hundreds of patients operated, the incidence of distant metastases is extremity low, and the reports probably reflect the higher awareness of this pathology.
Two kinds of distant metastases or extraneural metastases must be discerned, firstly the lymph node metastases, always at the same side of the primary and not always accompanying a cutaneous scar recurrence. The second is the rarely occurring hematogenous metastasis

Cervical Nodes

Cervical node metastases undoubtedly find their origin in craniotomy seeding of the scar. Tumoral recurrence has been observed in a number of cases.
From the review of the reported cases, we remark a majority of male patients and of patients with glioblastoma multiforme (table 12.9).

Pathways of Distant Metastases from CNS-tumors

Reviewing the literature cases, one observes different patterns. In the earlier reports, many patients did not undergo craniotomy and the spread was only found at autopsy. It is obvious that in the surgically treated patient, the normal anatomic barriers of spread have been opened at the site of surgery (table 12.10). Many patients, although indeed still rare, have experienced recurrence at the flap, with some developing cervical nodes, as already mentioned above.

[1] AFIP: Armed Forces Institute of Pathology, Washington, D.C.

Table 12.9 - Primary Tumors of the Brain
Reports with cervical metastatic lymph nodes

Author	Pat	Primary	Histology	Interv.	Site
Schejbal '62	F10	Pa-Te Ri	Glioblast	2 yrs	Ri. cerv
Braun 1968	F40	Front.Ri	Glioblast	3 yr	Cut Pr.Au
Pasquier'80	M43	ParaSag.	Astrocyt	3 mo	Ri. cerv
Merkel 1982	M19	Fr.Te.Ri.	Astrocyt	15mo	Cerv.mult
Potter 1983	M41	Front.Le	Glioblast	10mo	Le.subma
Dewar 1985	F44	Pa.Te.Le	Astrocyt	6 mo	Cut.Cerv
MacDonald	?36	??	Oligo	3 yrs	cervical
Zappia 1992	M39	Par.Ri.	Glioblast	1 yr	Cerv.mult
Gonzalez'93	M47	Pa-Oc Le	Glioblast	6mo	LeCe SC('
Steininger'93	M39	Pa-Te.Ri	Oligo	28mo	Ri.Cerv
Schröder '96	M49	'central'	Oligo(")	---	Ri.cerv.mult
Vural '96	M40	Pa-Te Ri	Oligo	3 yrs	Ri.SC
Wallace '96	M41	Front.Ri	Glioblast	3 mo	Cerv SC
Wallace '96	M39	Fr.Te Ri	Glioblast	5 mo	Pr.Aur.
AlRikabi '97	M4	Pa-Oc.Ri	Astro-IV	1 mo	Le.Cerv.
Jamjoon '97	M4	Occ.Ri	Glioblast	6 mo	Cerv.mul
Waite 1999	M40	Front.Le	Glioblast	2 yrs	Cerv mul

(") inoperable brain tumor, diagnosis on nodes
(') later also supraclavicular
Pa: parietal; Te: temporal; Oc.: occipital; Fr.:frontal; Cut.: cutaneous recurrence; Pr.aur..:pre-auricular; mult.: multiple; SC: supraclavicular; cerv.:cervical; Subman: submandibular.

Table 12.10 - Primary Tumors of the Brain
Pathways for Distant Metastases

1. Local implantation at surgery
2. Lymphatics draining the operation field
3. Hematogenous arterial or venous (Batson)
4. Shunting procedures

The opening of small veins at surgery makes it possible for tumor cells to reach the general circulation. This, however, can also occur through invasion by the tumor itself, breaking the blood brain barrier. Tumor invasion of the dural veins and direct extension towards the skull are indeed encountered at pathological studies. While hematogenous route is now accepted as the pathway for spread, we wonder that the frequently encountered solely skeletal spread should not be viewed as using Batson's venous plexus from the cranial vault or base on. Several cases have been reported where no pulmonary metastases were ob-served.
The advent of the use of several kinds of shunts in order to relieve intracranial hypertension allows tumor cells to migrate along the shunts towards other body compartiments.
In a systematic study of 22 consecutive primary gliomas, Cairns et al. encountered 8 cases or 36% of meningeal dissemination. A later review at the Mayo Clinics uncovered 42 cases.
A literature review in 1963 by Glasauer et al. revealed 89 cases of central nervous system tumors with metastases (mCNS). Demographic data are shown in table 12.11 and 12, though in the 89 patients, 17 pituitary carcinomas were included.

Bigner et al. reviewed 5 literature series and were able to identify three groups of cerebral primaries, according to the frequency of positive CSF-cytology (Table 12.13). The first group encompasses the malignant gliomas, the second groups contains 'unusual' malignant tumors and the third are the benign tumors, and will be discussed later.

Table 12. 11- Primary Tumors of the Brain
Patients with Distant Metastases
Literature Review by Glasauer et al. (1963)

	All	Meningeal	All Other
Adults	66 (20male)	35(20)	35 (20)
Children(')	23 (12)	4 (1)	19 (11)

Glial Tumors 27 (glioblastoma 17)
Primaries Supratentorial 25
Infratentorial 134

Anatomic Sites (number of sites 159)

Lung-pleura	33%
Lymph node(")	23%
Liver	14%
Kidney	6%
Bone	9%

Rare sites: Heart, Ovaries, Uterus, Bladder, Parotis, Thyroid, Thymus, Adrenal, Stomach, Colon
(') children below 16 yrs
(") all sites: cervical, mediastinal, abdominal.

Table 12. 12 - Primary Tumors of the Brain
Patients with Distant Metastases
Correlation Histology - Metastatic Site
Literature Review by Glasauer et al. (1963)

Medullobastoma (N=20)	Lymph nodes	25%
	Bone any site	35%
Meningioma (all)(N=64)	Lung and pleura	41%
	Lymph nodes	19%
	Liver	17%
Glioma-Ependymoma (N=47)	Lymph nodes	26%
	Lung and pleura	36%

Table 12. 13 - Primary Tumors of the Brain
Positive Cytology
Literature Review by Bigner et al. (1981)

Group I	Medulloblastoma	64.3%
	Astrocytoma I - II	21.7
	Astrocytoma III - IV	35.7
	Ependymoma	22.4
	Oligodendroglioma	29.1
Group II	Pineal Germinoma	4/12
	Choroid plexus carcinoma	1/1
	Malignant Teratoma	2/2
	Olfactory Neuroblastoma	1/1
	Meningiosarcoma	2/4
	Pineal Choriocarcinoma	1/1
Group III	Meningioma	11.7
	Craniopharyngioma	18.5
	Pituitary Adenoma	7.9

Reviewing only reported cases of gliomas (astrocytomas and glioblastoma), Pasquier et al. retrieved 72 cases, all satisfying the criteria of Weiss.
Of all mCNS, gliomas account for 40% in the literature, and glioblastoma and astrocytoma 25%. Further data are in table 12.14. Of the 72 cases, the metasta-ses developed without any craniotomy in 8, after craniotomy in 56, and in 8 after the placement of a shunt.

Table 12. 14 - Primary Tumors of the Brain
Astrocytoma and Glioblastoma only
Patients with Distant Metastases
Literature Review by Pasquier et al.1980

Adults 63
Children (<18 yrs) 9
Mean Age 35.8 (range 3.5-70 yrs)

Primary Site: Supratentorial 67
(left 39, Right 36, Bil.1)
Cerebellum 1; Pons 1, Spinal 1

Metastatic Sites

Lung - pleura	59.7%
Nodes (any site)	51.4%
(Cervical 62%, hilar 32%)	
Bone (any site)	30.5%
Vertebrae	72.7%
Heart	5
Adrenal	3
Kidney, diaphragm, mediastinum	2
Pancreas, thyroid, peritoneum	1

As table 12.11 clearly shows, bone and lungs are the most significant extranodal metastatic sites. Other sites have been reported but are very rare.
Widjaja et al. have reported a patient (M58) being treated for a temporal glioblastoma who developed only liver and spleen metastases. They found two other cases in the Japanese literature. Leifer et al. have reported on a M65 presenting simultaneously with a multifocal glioblastoma and liver metastases, diagnosed at autopsy. He had no surgery.
Recently, a case with endobronchial metastasis was reported, probably a pulmonary metastasis that had invaded the bronchi (Chung et al.).

The data on prevalence are more interesting, with the restriction that, as we shall see, treatment factors certainly have an impact in the incidence of extraneural metastases.
As far as medulloblastoma is concerned, two reviews are at hand: those of Kleinman et al. in 1981 and Rochkind in 1991. The number of cases included, however, shows that the reviews were limited as the first already had 101 cases, while Rochkind et al. collected only 119 cases ten years later.
The prevalence was calculated as 4.8% in a total of 686 cases, while the latter had 7.1% in 1025 cases, a similar incidence. The length of follow-up in the reported series was also certainly a factor influencing the prevalence data. The distribution of metastases is shown in table 12.15. No remarkable difference in

numbers between children and adults could be observed. They found also that at least 34 cases were reported in which metastases appeared after every shunt procedure.

Table 12. 15 - Medulloblastoma
Incidence of Extraneural Metastases
Literature Review by Rochkind et al. 1991

Site	Children N=89	Adults N=30	Astro+Glioblas
Bone	78%	77%	30%
Lymph nodes	33	33	51
Lung	11	17	60
Liver	15	10	22
Muscle	2	13	
Other	32	20	

Compared with glioblastoma, the incidence of bone metastases is three times more frequent in medulloblastoma, while the latter have much fewer pulmonary and fewer hepatic metastases.
The shunt seems associated with a significantly earlier appearance of metastases in both children and adults. In patients with a shunt the mean interval time was 13 months, while without shunt an interval of 24 months was recorded.

Kleinman et al. noted that in 53% of the 88 cases with extra-neural spread, there was clinical or radiological evidence of further involvement of the neuraxis, sometimes before the appearance of the extra-neural metastases.

A few cases of oligodendrogliomas with extraneural metastases have been reported. From a small series of 7 patients, MacDonald et al. claimed to be able to distinguish two patterns of spread. In the first group, the metastases 'started' at the scalp or/and in the cervical nodes, with subsequent spread towards bone and other organs. It is possible that the multiple craniotomies in these patients facilitated the spread.

Table 12. 16 - Oligodendroglioma
Distant Metastases
Literature Review by MacDonald et al. (N=21)

	MacDonald 1989 N=21	Baldus 1997 N=27
Scalp recurrence	8 (38%)	5
Regional Nodes	9 (43%)	11 (40%)
Hilar nodes	--	3
Bone	17 (81%)	19 (70%)
Lung - Pleura	--	3
Other	6 (28%)	(*)

(*) adrenal 1, liver 1, skull 1, paravertebral muscles 1

The second group had only multiple bone metastases without local or nodal spread and had not undergone a second craniotomy, only radiotherapy and chemotherapy.
The literature was reviewed by the authors and metastases data are shown in table 12.16. Remark that there are much fewer lung metastases than in glioblastomas, but a high incidence of bone as in medulloblastomas. Can we postulate a Batson phenomenon here?
If bone metastases are common in meduloblastoma and gliomata, bone marrow metastases have also been reported, apparently before further growth to overt bone metastases. The widespread situation is however clinically recognizable as anemia, particularly as leuco-erythroblastic anemia (30%) or pancytopenia (Newman et al.). Bone marrow punction or biopsy is of course diagnostic, while MRI is a non-invasive method to detect the bone marrow involvement.
Reviewing the literature, Hsu et al., found 15 cases reported, one from a low-grade glioma of the hypothalamus, 6 from supratentorial malignant astrocytomas and 8 from glioblastoma multiforme, one of whom infra-tentorial. Diffuse bone marrow infiltration was the presentation sign in a child with cerebral glioblastoma (Gamis et al.).

Ependymoma behaves like a glioma. Cases with metastases along the neuraxis or extra-neural have been reported. Up to 1990, there have been 108 cases reported out of 971, or 11.1% with spinal metastases. Already in 1972, Wolf et al. could retrieve 17 patients with intracranial ependymoma metastasized to the extraneural tissues and an additional 6 from the cauda equina.
Distant metastases were described in cervical and axillary nodes, lungs, diaphragm and mediastinum as well as intra-abdominal (Newton et al.).
Iwaszkiewicz mentions one case (F28) metastatic to the breast, three years after surgery for a cerebellar ependymoma.

Type 1 Presentation

Reporting on 27 patients where the first diagnosis of malignancy was made by an indicated CSF cytology, Bigner et al. mentioned 7 patients in whom a primary brain tumor was detected. It concerned 2 cases of medulloblastoma, 2 glioblastomas, 1 malignant micro-gliomatosis, 1 meningeal gliomatosis and 1 cerebral histiocytosis. We are not aware of other similar reports in the literature.
On the other hand, several cases where the distant metastases led to the diagnosis of an intracranial primary have been published (table 12.17).

Table 12. 17 - Primary Tumors of the Brain
Revealed by distant Metastases

Author	Pat	Site of M	Histology
Dolman 1974	F35	Parotid Node	Glioblastoma
Hulbanni 1976	M63	Lung vertebra	Glioblastoma
LoRusso 1988	M41	Bone Marrow	Astrocytoma
Gamis 1990	F12	Long bones	Glioblastoma
Myers 1990	F11	Diffuse Bone	Glioblastoma
Dubé 1996	M46	Bone D12	Astrocytoma

These are remarkable cases, in virtually every case

distant bone metastases were the first sign of an intracranial primary (Batson phenomenon ?).
A man (M37) presented with a recent parotid swelling and diplopia. CT demonstrated a large mass in the pineal and parapineal region. Cerebral problems led to death a few days later. At autopsy, a cerebral germinoma was found and the parotid tumor had the same histology (Pena et al.).

The Shunt and Extra-Neural Metastases

Several modes of shunting have been applied to relieve intracranial hypertension (fig. 12.3).

Ventriculo-atrial
Ventriculo-pleural
Ventriculo-peritoneal
Pseudo-meningocele - Peritoneal
Subdural-peritoneal
Cysto-peritoneal

It is obvious that in cases of tumor cell passage, a ventriculo-atrial shunt will deliver the cells towards the systemic circulation, engendering pulmonary metastases initially, while a ventriculo-peritoneal shunt will lead to intraperitoneal seedling and result either in solid tumors or malignant ascites or both. One must at first, however, remember that this technique has helped many hundreds of patients, while the risk for distant spread, although real, is indeed very low. There is no reason to render the system guilty, as every treatment method has its problems and still remains acceptable in view of the low incidence of complications.

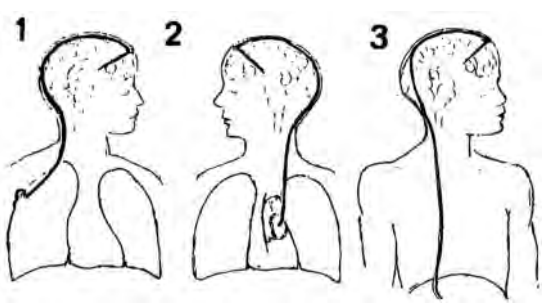

Fig.12.3 - The most frequently applied shunts to relieve hydrocephalus. 1: Ventriculo-pleural; 2: Ventri-culo-atrial; 3: Ventriculo-peritoneal

Table 12. 18 - Tumors of the Central Nervous System
Ventricular shunts and the Incidence of Metastases
Data of Berger et al. 1991

	No shunt	With shunt
All patients	5/263 =1.9%	3/152 =1.9%
Medulloblastoma	5/37 =13.5%	3/40 =7.5% (')

(')p=0.47, Fisher's exact test.

The problem of the risk of shunting was brought up by Berger et al. when they reviewed the outcome of 415 children with CNS tumors. Shunts were inserted in 152 children. Extraneural metastases occurred in 5 patients without any shunt, while 3 occurred with a shunt in place (Table 12.18), with a virtually identical incidence!
Further evaluation showed that all metastases occurred in the group of 77 medulloblastoma patients, but the difference was still not significant.
From these data, one can conclude that shunts do not appreciably favor the occurrence of metastases. We think also that the actually centralized treatments, the better documentation (imaging) and follow-up of the patients allows better detection of extraneural metastases. This become more evident when the sites of the metastases in these patients is examined. There is no difference in the metastatic sites between the two groups (fig. 12.4).

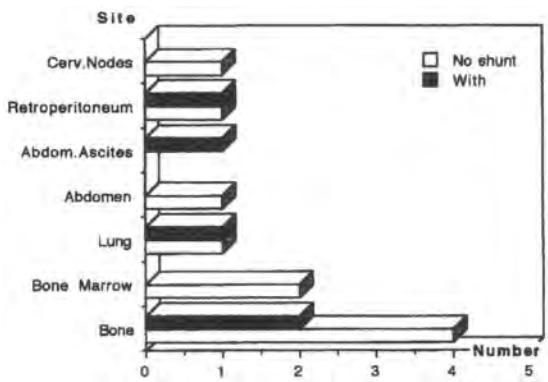

Fig.12.4 - Incidence of extraneural metastasis in brain tumors, depending on the presence of the shunt (drawn from data of Berger et al.).

Nevertheless, a review of the literature would suggest a relation between shunt type and the preponderant metastasis. With a shunt, most patients with medulloblastomas developed metastases in bone, bone marrow and lymph nodes. In patients with a V.P. shunt, few had metastases in intra-abdominal structures without any extra-abdominal sites, and lung and pleura in patients with a V.A.-shunt.

Table 12.19 - Tumors of the Central Nervous System
Abdominal Metastases reported after V.P.Shunt (N=58)
Literature Review by Richter et al.

Germinoma	27.5%	Teratocarcinoma	3.4%
Medulloblastoma	18.9%	Ependymoma	3.4
Endoderm.Sin.Tu	10.3%	Oligodendrogl.	1.7
Astrocytoma	8.6	PNET	1.7
Pinealoblastoma	6.9	Sarcoma	1.7
Glioblastoma	6.9	Teratoma imm.	1.7
Melanoma	5.2	Pineal NOS	1.7

Malignant gliomas prefer to metastasize primarily in lungs, pleura and lymph nodes, rarely the abdomen. Pineal germ-cell tumors frequently involve lung and lymph nodes in the presence of a shunt; some will have also only abdominal metastases. There are indications however that an aggressive chemotherapy should almost prevent the occurrence of extraneural

metastases (Berger et al.).
Reviewing the literature on abdominal metastases after implant of a ventriculo-peritoneal shunt, Richter et al. noted that germinomas had the highest number of reported cases (table 12.19).
In view of the relative rarity of the germinoma, this histology type apparently has a propensity to proliferate within the abdominal cavity. But the reader should remember that in view of the large number of patients submitted necessarily to the shunting procedure, the incidence of metastases is relatively low.
We are aware of only one optic glioma reported to have metastasized to the abdominal cavity after a VP-shunt was installed (Trigg et al.).

Metastases from Pineal Tumors

The pineal region is the site of tumors either specific to the pineal gland (pinealomas), or more frequently extragonadal germ cell tumors. They occur most-ly in young people. The proximity of the tumor to the ventricles and the CSF-circulation is a risk factor to an intra-cisternal dissemination. They can allow wide-spread intradural seeding with tumoral masses all over the CNS downwards to the cauda equina.
Extraneural metastases are regularly reported in small series or as case-reports. It is very probable that the distribution of distant metastases has not changed since the review of Galassi et al. in 1984. They observed a certain degree of correlation between the histology type and the metastatic sites (Table 12.20).

Table 12.20 - Malignant Tumors of the Pineal Region
Metastases according to histology
Review of Galassi et al. 1984

Site	G N=7	Ch N=5	Y N=2	EC N=1	P N=1
Lungs	4	5	2	1	1
Lymph No	3	1	-	-	1
Peritoneum	1	-	1	-	-
	Bone 1	Liver 1		Ur.Blad 1	
	Lumb.Muscle 2	Kidney 1		Pancreas 1	
	Cerv.Spine 1	Rib 1			

G: Germinoma; Ch: choriocarcinoma; Y: yolk sac tumor;
EC: embryonal carcinoma, P: pinealoblastoma

As one would expect, the lung is the most frequent metastatic site, especially in choriocarcinoma. Lymph node metastases were observed in 11/16 or 68% of the patients.

Metastases from Meningioma

A frequently discussed problem on metastases is the definition of malignancy of the meningioma.
Malignancy can be defined at histology, where the associated features may include cellularity, pleomorphism, invasion, mitotic activity, n-crosis, sarcoma-like areas, sheeting, prominent nucleoli and an hemangiopericytic pattern (Younis et al.). Based on these features, the authors divided the 'malignant' meningiomas into four groups, in order of severity the atypical, the malignant, the meningeal sarcoma and the hemangiopericytoma. Of the 44 'malignant' meningiomas retrieved from their pathology file, metastasis was found in 1/6 of the atypical, in 2/12 of the malignant, in 1/3 sarcomas and 2/4 hemangio-pericytoma. The total number was 5 or 11%.
Metastases have been observed in histologic benign meningiomas, but as can be expected, most frequent in histologically malignant meningiomas. The inadequacy of the histology has led Prayson to limit the malignancy to the meningiomas with overt metastases, either intradural or extraneural, a definition also used for several 'endocrine' malignancies.

Pathways

The pathways of spread is another discussion point. Invasion of vascular structures can theoretically lead to vascular spread and the frequent involvement of dural sinuses may be a factor. There is, however, only a minor number of cases that will develop distant metastases. Histological infiltration of the sagittal sinus was observed in 34 of 246 (14%) of intracranial meningiomas, but in only 1 patient were extracranial metastases observed (Simpson et al.). Seeding through the cerebrospinal fluid pathways or distant intracerebral metastases are much less frequent than extraneural metastases. A patient (M34) has been reported with leptomeningeal spread from a ventricular meningioma (Kleinschmidt et al.).

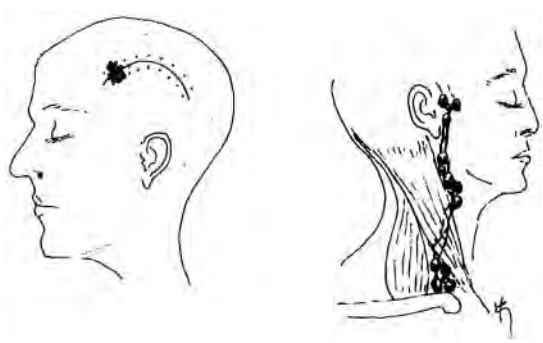

Fig.12.5 -Recurrences at the operative scar (left), metastases along the cervical lymphatic chain (right)

Incidence

The incidence of extraneuraxial metastases in meningioma is estimated to be less than 0.1% of the patients with this tumor.
Of 23 histological malignant meningiomas, Prayson could only find 6 or 26%. If the two with only skin metastases are excluded, the incidence will be 17%.
In a series of 396 consecutive intracranial meningiomas treated between 1976 and 1993, only 3 or less than 1%, developed distal metastases, of which 1 had only intradural metastases (Enam et al.). This stresses

the low incidence of the metastasis in this tumor.
At the Mayo Clinics, only 3 cases with lung metastases were seen in a series of 2000 meningiomas.

Sites of Metastases

The most frequent sites are the lung (60%), liver (30%), cervical lymph nodes (18%) (fig. 12.5), and bone (11%). Rare observations of metastasis in the kidneys, the urinary bladder, thyroid, breast, thymus, heart, skin, vulva, adrenals and even ocular fundus have been reported.
Up to 1991, 113 cases of extra-neural metastases from meningiomas had been reported (Salcman). Most were accompanied by a local recurrence.

Imaging methods such as CT cannot reliably distinguish the malignant from the benign meningiomas. A number of features can point towards malignancy including mushrooming, the presence of a prominent part extending away from the globus, and peritumoral edema. Osteolysis of the cranial bone is not a definite sign of malignancy. Contrast enhancement and tumor density are not reliable aspects to separate both groups. MRI seems to have better accuracy, but this has not been confirmed by several authors.

The interpretation of pulmonary nodules must be cautious. Primary benign meningioma of the lung have been reported, but are always a solitary lesion compared to the multiplicity in case of metastases. Most metastases are detected several years after resection of the primary, but as can be seen in table 12.21, a number of pulmonary nodules were the revealing sign of an asymptomatic intracranial meningioma.
The mean interval between first diagnosis and observation of metastases is about 6 years, but very long intervals are not uncommon, even up to 24 years (Adlakha et al.). We have compiled a non-exhaustive list of reported cases of non-pulmonary metastases (table 12.22) (only available reports).

Table 12.21 - Meningioma Cerebri
Pulmonary Metastases - Selected References

Author	Pat	Primary	Site of M	Interv.
Kruse 1960	M19	Ri.Par.Occ	Lung	5 yrs
Kruse 1960	M55	Midfrontal	Lung	(Autopsy)
Noto 1961	F47	Le.Fro.Tem.	Lung	3 yrs
Palacios '75	F63	Le.Parasag	Lung	3 yrs
Peck 1976	M36	Ri.Fr.Par	Lung	3 yrs
Aumann '86	F45	Le.Frontal	Lung	5 yrs
Stoller 1987	F63	Le.Frontal	Lung	18 yrs
Som 1987	M50	ParaSagitt	Lung mult	18 mo
Fukushima'89	M40	Le.Occip.	Lung mult	10 yrs
LeMay 1989	F56	Sphen.Wing	Lung	16 yrs
Kodama '91	F61	Cerebellum	Lung (')	19 yrs
Tao 1991	M32	Ri.Frontopol.	Lung	13 yrs
Hamant '92	F31	Ri.Parasag.	Lungs	11 yrs
Hishima '95	F25	Ri.Pariet.	Lung mult	Reveal
Adlakha '99	F17	Le.Par.Occ.	Lung	2 yrs
Adlakha '99	F70	Le.Fro.Paras	Lung	R eveal
Adlakha '99	M30	Le.Parasag.	Lung	6yrs

The case reported by Kamiya et al. is one of the 3 cases of intraventricular meningiomas reported to have metastasized via the CSF (Kleinschmidt et al., Strenger et al.).
A woman (F61) at first surgery for two cerebellar mengiomas has been reported by Koda et al., as presenting 19 years later. She complained of thoracal pain, revealing multiple lung metastases. Two and a half years later, a laparotomy had become necessary, during which in total seven metastatic tumors were excised at several locations.

Table 12. 22 - Meningioma Cerebri
Non-Pulmonary Distant Metastases
Case reports from literature

Author	Pat	Primary	Site of M	Interval
Miller 1972	M45	Front-Tem	Mediast.	2.5 yrs
Lowden '74	F36	Le.Parasag.	Breast	8 yrs
Palacios '75	F30	Spinal Cord	Lung-Liver-Bone	4yrs
Jestico '76	M47	Ri.Parasag	Liver	6 yrs
Anderson'80	M32	Occipital	Bone (mult)	2 yrs
Wu 1985	F56	Le.Occip.	C3+mass	10 mo
Tanabe '84	M65	Parasag.	Pancreas	15 yrs
Noterman'87	F51	Temp.Par Le	Cerv.Node	9 yrs
Som 1987	F53	Ri.Sphenoid	Bone-Lung-Liver	6mo
Strenger '87	F61	3rd Ventr.	Brain	Simult
Kamiya '89	M67	Front.Temp.	IntraD.ExtraM	6 mo
Leighton'91	M55	Ri.Fron.Par.	Cerv.node	9 yrs
Celli 1992	M11	Ri.Parasag.	Parotid gl	12 yrs
Tominaga'94	F41	Ri.Parasag.	C2	3 yrs
Palmer 1994	M55	Fossa Poster	L5-lung	12 yrs
Rawat 1995	M49	Ri.Occip.	IL.+Glut.mu	3 yrs
Rawat 1995	M41	Ri.Fos.Post	Ri.femur	2 yrs
Vinchon '95	M44	Fossa Ant.	Meningeal	11 mo
Enam 1996	F73	Front.Parie	Liver	9 mo
Enam 1996	F52	Sphenoid	Femur L2	4 mo
Koyama '97	M55	Occipital	Pancreas	17 yrs
Figueroa'99	F50	Le base	Lung Liver	5 yrs
Kros 2000	M13	Le.Fos.Post.	Pleura	1 year
(') see text				

Recently, another case was reported by Meinsma et al. A 19-year-old man was diagnosed with a meningioma within segment C3-C4. Six months later he was found to have an intraspinal metastasis at L3 and in the fossa posterior.

A very uncommon occurrence is that of hypoglycemiacrisis due to metastatic meningioma. We are aware of three such reports. Two patients had liver metastases (Yoshida et al.) and the other had a large retroperitoneal mass. Insulin and other hormones were not concerned, the most probable reason being caused by an increased glucose consumption caused by the metastatic tumor (Phuphanich et al.).

Causes of Death

Very few studies have been reported of 'total-body' autopsies of patients who have died of primary cerebral tumors. Most will obviously have died as a result of the extensive or strategic destruction within the central nervous system, impending normal live functions.

Reporting on 117 consecutive cases of glioblastoma multiforme, Silbergeld et al. made many interesting observations. Twenty (17%) of these patients were not known to have a primary brain tumor before autopsy (table 12.23).

It must be concluded that death from brain tumors, as for all tumors, is multifactorial. Herniation, mostly due to tumor expansion, is found in 61%, but other factors could precipitate death. The authors seemed surprised at the high number of multiple tumors and the number of cases with brainstem invasion.

Table 12. 23 - Primary Tumors of the Brain
Findings at autopsy - All Glioblastoma Multiforme
Data of Silbergeld et al. (N=117)

Pathology			
Unknown before autopsy	20		
Post mortem evidence of herniation	71		
Pontine hemorrhage	16(')		
Distortion of brainstem	29		
No brain abnormality	26		
Multifoval tumors	20		
Brain stem invasion	18		
Potential cause of death (no data!)			
Herniation			
Postoperative death (30 days)			
Systemic illness (pneumonia, infarctus)			
Invasion of brain stem			
Irradiation (neutron) sequellae			
Death from 1 cause	53		
Death from 2 causes	51		
Death from more	5	Unknown	8

Overall Lessons

While distant metastases of primary cerebral tumors are rare, theyt offer the opportunity of finding more about the nature of these tumors. The shunting procedure is still an important measure for relieving patient from the increased intracranial pressure and has a low risk of distant metastases, although strict follow-up is mandatory.

METASTASES from PITUITARY CARCINOMA

The most common tumors of the pituitary gland are adenomas. They are histologically benign tumors. Located and confined within the bony sella tursica, they enlarge at a slow pace. The demarkation with the normal pituitary tissue is usually distinct but not delineated by a capsule. The various different functional classifications will not be discussed here.

Pituitary adenomas account for about 10% of all intracranial neoplasms.

Some adenomas, however, have a clear expansile proneness and infiltrate surrounding tissues, including dura, bone, vascular structures, cranial nerves and sinuses. However, there are no other distinct loose tumors. The tumor infiltrates along the anatomical structures, mainly in a tongue-like way. These are called invasive pituitary adenomas.

Labeled as pituitary carcinomas, these tumors clearly send tumor cells elsewhere within the cranial or/and intrathecal volume, but can also disseminate extraneurally. At histology, a diagnosis of malignity is not possible, since the term 'carcinoma' is applied only in the presence of intra- or extracranial metastases.

Invasive adenomas can extend in several directions according to the different anatomic 'walls' (Krueger et al.). This process is better described by the term 'extension' than invasion.

1. Extension into the sphenoid sinus and nasopharynx
2. Hypothalamic extension
3. Frontal extension
4. Temporal extension
5. Involvement of the cavernous sinus
6. Posterior subtentorial extension

1. Extension into the sphenoid sinus and nasopharynx. The erosion of the sellar floor with ex-tension to the sphenoid sinus is the most common observed. There have been rare reports of rhinorrhea, and filling of the nasopharynx is also rare.
2. Hypothalamic extension. If the tumor extends upwards and backwards behind a fixed chiasm, the hypothalamus is displaced. Peculiar is the rarity of hypothalamic symptoms such as polydipsia or temperature regulatory disturbances unless invasion or destruction occurs. An upward growing adenoma may compress and dama-ge the optic nerves and chiasm. It can invade the third ventricle, Hydrocephalus with headache and papilledema is observed when the foramen of Monroe is blocked.
3. Frontal extension. Forward and upward extension in front of a fixed chiasm can compress and separate either the olfactory bulbs or the frontal lobes. Personality changes, epileptic seizures, olfactory and visual symptoms are seen in these patients.
4. Temporal extension. When the adenomas extend in the lateral direction, between the sinus cavernosus and the chiasm, they invade the middle fossa, pushing on the optical tract and the temporal lobe causing temporal lobe epilepsia with olfactory aura and homonymous hemianopsia.
5. Involvement of the cavernous sinus. When the adenoma pushes on the lateral wall, extrensic pressure on the sinus cavernosus can occur. Further invasion of the sinus and Meckel's cave will cause some irritation of the trigeminus. Ocular palsies will soon follow, with diplopia, pain and vision disturbances.
6. Posterior subtentorial extension. Extension towards the cerebellopontine angle, eventually with the erosion of the petrous apex is the rarest form. Signs of cerebellum dysfunction and several cranial nerve palsies with bilateral papilledema will occur.

Previously, extension was deduced from neurological and faint radiological observations. The advent of CT and later of MRI has revolutionized diagnosis of the extent of the adenomas.

The SIPAP-classification of the extension of Adenomas as seen at MRI (Edal et al.)

SIPAP is the acronym for Suprasellar, Infrasellar, Parasellar, (Right and Left) Anterior and Posterior.
To each a grade can be ascribed, with a SIPAP-classification for each adenoma, f.i. 2-1-1-4-0-0.

Suprasellar
- Grade O: The adenoma does not bulge into space
- Grade 1 : The adenoma bulges into Suprasellar cistern , without reaching the optical chiasm;
- Grade 2 : It reaches the optical chiasm, without displacing it;
- Grade 3 : The adenoma displaces and usually stretches the chiasm to a variable degree;
- Grade 4 : Obstructive hydrocephalus of one or both ventricles caused by tumor extension.

Infrasellar
- Grade 0 : Intact floor of sella
- Grade 1 : Focal bulging of the adenoma as an indirect sign of perforation of the dura and the floor of the sella;
- Grade 2 : Tumor penetration beneath the sphenoid sinus.

Parasellar (Knosp-Steiner)
- Grade 0 : normal condition
- Grade 1 : reaches the intercarotid line;
- Grade 2 : reaches the intercarotid line and the carotis;
- Grade 3 : passes the intercarotid line
- Grade 4 : total encasement of intracavernous carotid artery

Anterior Extension
- Grade 0 : No tumor extension;
- Grade 1 : The adenoma grows into the anterior fossa

Posterior Extension
- Grade 0 : no growth of the adenoma behind the clivus;
- Grade 1 : tumor growth behind and inferior to the dorsum sellae or the clivus, through the diaphragam of sella and into the prepon-tine subarachnoid space, with or without destruction of the dorsum sellae.

The proportion of gross invasion was examined by Scheithauer et al. for each type of adenoma, according to histology and functionality. They reviewed 365 patients treated at the Mayo Clinics (1980-1985).
There is apparently some correlation between frequency and nature of invasiveness and the functional type (Table 12.24).

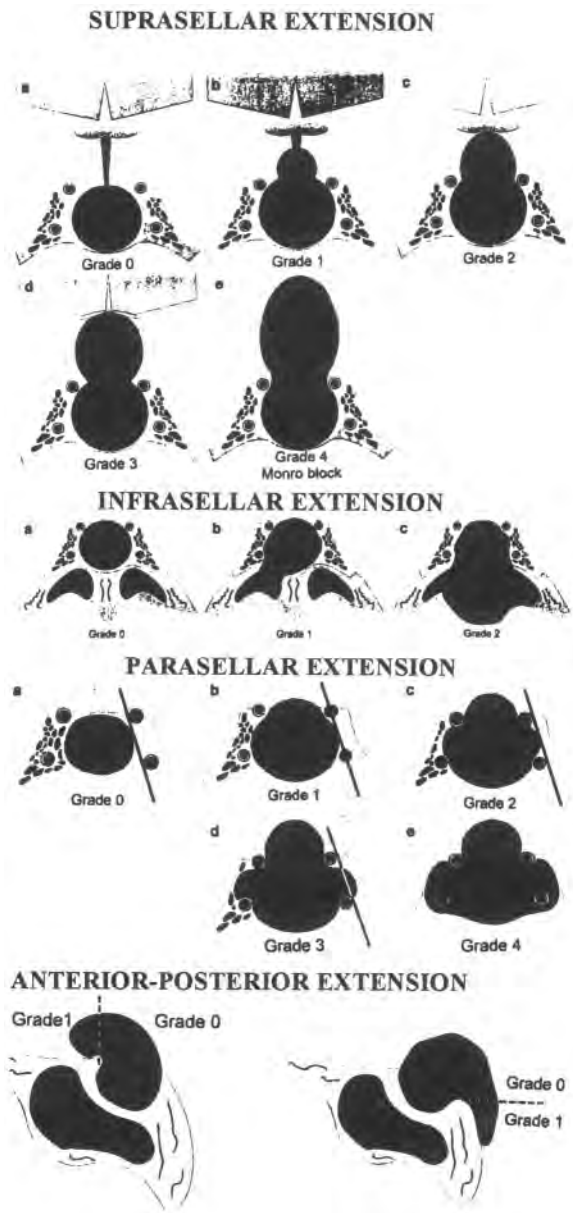

Fig.12.6 - The SIPAP-classification at imaging of pituitary adenomas as proposed by Edal et al.

Table 12. 24 - Invasive Pituitary Adenoma
Correlation with functional type
Data of Scheithauer et al. 1986

Type	N	With Invasion
Cushing	60	15%
FSH-LH cell	32	21
Mixed GH-PRL	35	31
Null-cell	93	42
GH-cell	23	50
Nelson	20	50
Prolactin	24	52
Plurihormonal	63	52
TSH-cell	4	75
Silent ACTH-cell	11	82

Further spread within the CNS result from cells losing contact with the primary, following nervous tracts or vessels or transport by the CSF- circulation. As can be seen from Table 12.26, the transport goes down to the cauda equina, as has also been mentioned in relation to other cerebral primaries.

The diagnosis of intracranial spread is obtained by CT or preferably MRI. In old case reports the diagnosis of spread was only obtained at autopsy. CSF cytology apparently produced many negative results, though endocrinologic dosage of the serum and CSF can be relevant, but more as a marker of the response to the various different treatments.

Distant Metastases - Pathways

The tumors with the cranial or intrathecal cavity or/and extraneural dissemination are considered pituitary carcinoma. The literature reviews do not make distinction between aither.
According to Pernicone et al, this definition is unsatisfactory in view of the histological impotency. They suggest that increased mitotic activity, proliferation indices and the presence of p53 staining might be a better 'base'.

A review by Saeger et al. found that of 2,342 pituitary tumors, 0.13% were labeled carcinoma. Up to 1996 at least 67 cases had been reported. Most patients were middle-aged though the range is large, between 7 and 75 years. There was no gender preponderance. The hormonal clinical features of these tumors are listed on table 12.25.

Six patients with pituitary carcinoma represented 0.2% of the 3000 pituitary adenomas resected between 1955 and 1994. The authors grouped these cases with 9 patients from other institutes. Of the 15 cases, eight had extraneural metastases, mainly bone, with 3 nodal and 8 had intrathecal spread. Four patients had only extraneural spread (Pernicone et al.).

Table 12. 25 - Pituitary Carcinomas
Hormonal Clinical Features of the Reported Cases
Modified from Blevin et al.

Endocrinologic		Metastases	
Nelson syndrome	6%	Intracranial	48%
Hyperprolactinemia	22	Spinal Cord	21
Acromegaly	13	Visceral	31
Nonfunctional	39	Nodal	13
Cushing syndrome	18	Skeletal	13

A review made in 1995 showed that the liver was the main metastatic site, in about 50% of cases. In half of them, it was the only site. Pulmonary metastases, as well as those in bone and lymph nodes were less common. There is no obvious explanation for this paradoxal distribution.
Metastases in the kidney, mediastinum, heart, muscles and other organs we rare. Worthwhile mentioning is that several metastases were only disclosed at autopsy, as they were asymptomatic.

Table 12.26 - Pituitary Adenomas
Intracranial - Intrathecal Metastases
Reported Cases

Author	Pat	Type	Site of metastasis
Newton 1963	M15	Chromoph	Midbrain, pons, Cerebell, mening.
Newton 1962	F27	Acromeg	Hippocamp..men.
Madonick 1963	M75	Chromoph.	A: mass opt.ch. Le.temp.lobe, 3d.V.
Braun 1964	F23	Adenoma	A: frontal lobe
Epstein 1964	M29	Chromoph	Cord-Caud.Eq.
Fleischer '72	M43	'Adenoma'	Base-Pons
D'Abrera 1972	F24	'carcinoma'	A.submand.node A: cerebellum
Ogilvy 1973	M54	Chromoph	CSF+, Parietal
Ogilvy 1973	F49	Acromeg	Mass CPA, several nodules in fos.post
Ricoy 1974	M47	Chromph	MassParietal lobe
Martin 1981	F31	Prolact	Cerebellum
Cohen 1983	M70	Prolact	Mass CPA
HoiSangU 1984	M62	Prolact	A: leptomeningeal Le.parieto-Occip
Gatti 1984	F32	ACTH	Cerebell.-Le hemi
Papotti 1984	F32	ACTH	Le.hemisphere - fossa posterior
Landgraf 1985	F44	Prolact	Cauda Equina
Gasser 1985	M28	Prolact	Several intracranial
Plangger 1985	M28	Chromph.	CT: tempor.,pariet Mult.nodules dura
Hashimoto '86	F48	GH-secr	Pons, Occip.CPA nodules over cord
Kuroki 1987	F46	Chromoph	Mult.Intracranial
Asai 1988	F28	GH-secr	Tu Ri.Frontal
Muhr 1988	M26	Prolact	Mult.Intracranial
Popovic1991	M47	Prolact	Anter.Fossa
Popovic 1981	F56	Prolact	Up to brain stem
Kamphorst '92	M45	(Ectopic)	Mult.Intracranial
Stewart 1992	M49	GH-secr	Nodules all-over
Tonner 1992	F52	ACTH	Cerebellum
Yamashita 1992	F35	Acromeg	Nodul.along cord
Petterson'92	M40	Prolact	Ventr.,CPA, Surfac
Assies 1993	M63	Prolact	Ri.Front.Lobe
Long 1994	M70	Prolact	Le.Frontal lobe
Giordana '94	M28	Chromph	A: Cer.pont.angle Mult.nod.subdura
Taylor 1994	M40	Adenoma	nodules Li.pariet-frontal(2x)
O'Brien 1995	F32	Adenoma	Cerebellum
O'Brien 1995	M48	Prolact	Frontal lobe
Frost 1995	F43	ACTH	Cauda Equina
Dayan 1996	F42	Acromeg	Intrad.C3-T1
Rockwell 1996	M50	Prolact	Mult.Intradural nodules C1 to L3
BayIndir 1997	F32	Prolact	Intradur.T10-T12 Frontal lobe
Popadic 1999	M51	Prolact	Intraspinal S1-S2
McCutcheon '00 (A: autopsy)	F20	Gonado	Sin.Cav. Frontal

If only those cases after 1970 are considered, fewer non-functional tumors have been registered, probably because of better clinical and histochemical studies.

Remarkable is the relatively high number of ACTH and prolactin secreting tumors. If the tumors are related to the number of adenomas, the ACTH tumors have the highest propensity to systemic spread, with 67% within the liver. PRL carcinomas have more cerebrospinal metastases (Pernicon et al.).
The mean interval between diagnosis of the adenoma and the occurrence of metastases was 6.6 years (range 4mo- 18yrs). For ACTH tumors this interval amounts to 9.5 yrs (3.5-18 years) and for Nelson syndrome still longer (15.3 years) (Pernicone et al.).

Table 12.27 - Pituitary Carcinomas
Site of ExtraneuralMetastases
Reported Cases

Author	Pat	Type	Site of metastasis
Sheldon 1964	M26	Cushing	Liver
Geroulanos '69	M74		Liver - several bone
Queiroz 1975	F38	Cushing	Liver nodules (2)
Moore 1976	M21	ACTH	Brain, cord, liver
Kaiser 1983	F27	Cushing	Liver, lung, bone
Myles 1984	F56	GH	Bone
Nudleman '85	F60	Carcinoma	A:lung,liver,kidney
Scheithauer'85	F60	Prolact	Bone (diffuse)
Casson 1986	M58	Cushing	Liver,Node, Bone(dif)
Gabrilove '86	M28	ACTH	Liver,heart, cord
Luzi 1987	F64	Inactive	A:subarach. stem cervical cord Cervical Nodes
Mountcastle '89	M56	Acromeg	Subarach.'drop' Cervical Nodes
Nawata 1990	M53	CRH-ACTH	Liver, lung
Atienza 1991	M34	Prolact	Bone: C2, C5, T1 Mult.bilat.lung
Levesque '91	M25	Cushing	Submand.Node
Mixson 1993	F30	TSH	Mult.lung, pleura Sacral mass, liver
Walker 1993	M32	Prolact	Orbit,liver,lung,Nod
Walker 1993	M48	Prolact	Vertebral column
Walker 1993	M49	Prolact	Bone, lung, mediast
Cusimano '94	M54	Adenoma	Rib, SI jt, lumbar Calvaria multiple
Jamjoon 1994	M59	Chromoph	Cerv.Node
Cartwright '94	F28	Chromoph	Cerv.Node
Cartwright '94	F46	Not stated	Intraspinal - Node
Lubke 1995	M60	Cushing	Bone, muscle
Gollard 1995	F33	Prolact	Le.Ovary, nodes iliac and pelvic
Saeger 1995	M62	Prolact	Liver (1 big, 2 sm)
Greenman '96	F37	Acromeg	Cerv.node, mult.
Garrao 1997	M47	ACTH	Vert.T7, T8, T10, L1 Cord compression
Lormeau 1997	F18	ACTH	Liver
Hurel 1997	F54	Prolact	Node subm. cerv Vertebr.thoracic
Masuda 1999	M59	ACTH	Mult.lung nodules Node mediastin.
Richter 2000	F57	ACTH	liver, Bone T11,T12

Distant or extraneural metastases can be explainedin the same terms as the other intracerebral tumors.
Tumor invasion or surgical violation of the basilar cisterns provides access to the cerebrospinal fluid and the subarachnoidal space. In many cases surgery or possibly even the placing of a shunt can be considered as a factor favoring dissemination.
The very low incidence in view of the large number of patients with pituitary adenomas, surgery or placement of shunts cannot be considered to be contraindicated.
Cases reported with metastases within the CNS are shown in table 12.26 while those withn extraneural metastases are in table 12.27.
The access of tumor cells to systemic circulation could occur via the sinus cavernosus and towards the sinus petrosus and jugular vein.
Lymphatic invasion within the sphenoid sinus may explain metastases in the cervical nodes.

ACTH-producing hypophyseal carcinomas are the ones least likely to spread extraneurally. Gatti found six cases in the literature before 1975.

We are aware of only three cases of gonadotropin secreting pituitary carcinomas.

Craniopharyngioma

Craniopharyngiomas represent about 2% of all intracranial tumors. They are benign but aggressive neoplasias mainly located in the sellar or suprasellar area. They extend rarely to the anterior, the middle or posterior cranial fossa (Kristopatis et al.) or to the nasopharynx.
Brain invasion is observed in one third of the adamantinous tumors, but in only 10% of the squamous papillary type. The frequency is higher in the pediatric group (Weiner et al.). It can affect the visual pathways, but also the frontal lobe, the strio-capsulo-thalamic areas, the mamillary bodies and the limbic system (Yasargil et al.). Extraneural metastases have not been reported, to our knowledge.

METASTASES from MALIGNANT TUMORS of the SPINAL CORD

Malignant tumors of the spinal cord are rare, Nevertheless, the several reports that have appeared, have demonstrated their aggressive character within the craniospinal space.
Several cases have been described in young children (Bell et al.).
Reviewing the literature up to 1986, Sarabia et al. could retrieve only 19 cases of medullary gliomas that metastasized through the subarachnoidal space to the cerebral or cerebellar space. They added one case where a intramedullary tumor (astrocytoma) situated at the T11-L1 level subsequently (6 months) metastasized to the ventricles, with invasion of the corpus callosum, the chiasm and the basal cisterns. In all the reviewed cases, the interval was shorter than 1 year. Data on the site of the primary were not retrieved however.

Leptomeningeal spread was reported in three patients with spinal cord tumors (Bell et al.), all astrocytomas (table 12.28). It is a very rare complication as only a few had previously been reported. Another small series was reported by Civitello et al.

Table 12.28 - Spinal Cord Tumors
Leptomeningeal spread

Bell	M13	T2-T6	Anapl.astrocytoma	2 mo
Bell	M25	C3-C7	Fibrill.astrocytoma	4 mo
Bell	M3	C2-C7	Low-grade astroc.	4 mo
Hely 1985	??19	Thor	Astrocytoma	21 mo
Civitello '88	??3	Cerv	Fibrill astrocytoma	18 mo
	??3	Cerv	Fibrill astrocytoma	12 mo
	??6	Cerv	Fibrill astrocytoma	5 mo
Rossberg'88	M73	T5-T6	Glioblast.Mult.	Simult

We are aware of two cases of brain stem astrocytoma with extraneural metastases. The patient (M23) described by Choi et al. presented simultaneously with increased intracranial pressure and lower back pain due to diffuse skeletal metastases. Castro et al. have reported on a 4-year-old girl with a brain stem astrocytoma. She was helped with a ventriculo-peritoneal shunt. One year later she developed intracranial and intra-peritoneal metastases.
An intramedullary glioblastoma at T12 in a M45 metastasized within 10 months all over the spinal cord, but also to within the cranial cavity, the septum, the lateral ventricle, both optic nerves and the surface of the cerebellar hemispheres (Andrews et al.).

METASTASES from NEUROBLASTOMA

Neuroblastoma can be defined as a malignancy of the sympathetic nervous system, more specifically from embryonic neuroblastic tissue.
It is one of the most common malignancies in childhood and the most frequent non-systemic tumor in children after primary CNS-tumors.

It can originate at every site where the sympathetic nervous chain is present, but the most frequent site is the abdomen, mainly from the adrenal (60%). Other frequent sites are the thorax and the pelvis. Its spread all over the body can make it difficult to locate the site of origin, though metastases can be defined as sites with neuroblastomas where no sympathic tissue is normally present.

Previously more confined neuroblastomas were named
Hutchinson- type confined to bone metastases,
Smith-type, confined to skin metastases and
Pepper-type, confined to liver metastases.
A very large series of 253 cases has been published which details the presenting symptoms and signs of all cases treated in Denmark between 1943 and 1980 (table 12.29).

Table 12.29 - Neuroblastoma - 1943-1980
Symptoms and Signs at Diagnosis (N=253)
Data of Carlsen et al. 1987

	Complaint	Finding
Fatigue, irritability, pallor, poor general condition	48%	40%
Inexplicable Fever	31	9
Anorexia, Weight loss	26	--
Swelling of Abdomen	16	24
Abdominal mass	13	53
Enlarged Liver	--	12
Respiratory Symptoms	13	9
Routine Chest X-ray	4	--
Paraparesis	12	12
Bone pain - metastases	23	--
Periorbit.ecchym.-Exophtalm.	17	18
Peripheral Nodes	9	26
Skin Metastases	9	--
Horner Sy - Heterochromia	2	3
Watery Diarrhea Syndrome	2	2
Dancing Eye syndrome	2	2

It will be noticed that half of the patient had vague complaints such as fatigue, malaise or irritability. More than 20% had bone pain as the presenting complaint.

Distant Metastases

For the same patient group, the authors were able to report on the widest spread of the tumors observed, since not all patients had an autopsy (table 12.30). The tumor seems to spread equally frequently by lymphatic vessels to distant nodes and by blood to bone and/or bone marrow. Only in widely disseminated 'bone' cases, will metastases appear in lungs, meninges, brain gonads and spleen.
They made another important observation. In patients treated with chemotherapy, there was a clear indication of a higher incidence in several metastatic sites. The likely explanation for this is the longer survival, allowing more extensive involvement of different 'sanctuaries'.

Table 12.30 - Neuroblastoma
Maximum Spread Observed in 253 patients
Data of Carlsen et al.

LocoRegional		Distant	
Primary across mid	54%	Bone Marrow	49%
Dumb-bell	13	Bone cortex	43
Prim.across diaph.	9	Liver	28
Contralateral N	61	Orbita	27
Distant Lymph N	49	Lung	21
		Skin	11
		Meninges	6
		Brain	4
		Gonads	4
		Spleen	1

Patients with metastases are allocated to stage IV, as in all other cancers, but in neuroblastoma an additional stage IV-S is defined, where remote metastases are confined only to one or more of the following sites: liver, skin, bone marrow, without radiographic evidence of bone metastases on complete skeletal surveys.
When only nodes are anywhere involved, Stage IV-N has been proposed.

In view of the somewhat better treatment results or prognosis of stage IVS, there has apparently been more interest in this stage and comparably more data on it.

In 45 patients with stage IVS, there were 77% liver metastases, 41% bone marrow and 14% skin metastases, with a lot having more than one site involved (Hachitanda et al.).
Reviewing several series in the literature up to 1997, VanNoesel et al. tabulated the distribution of the different metastases. After extracting the data, we found the following distribution (table12.31).

Table 12.31 - Neuroblastoma Stage IVS
Metastatic site Distribution from Literature (N=121)
from data of VanNoesel et al.

Liver only	72	(59.5%)
Liver and skin	17	
Liver and bone marrow	19	
Liver, skin and bone marrow	4	
Skin only	3	
Bone marrow only	4	
Bone marrow and skin	1	
Skin and mediastinal node	1	

Eight patients with stage IV-N metastatic to the left supraclavicular nodes were reported by Abramson et al. All ages from 0.5 to 10 were concerned. The primary was located in the adrenal but side was not stated.

Table 12.32 -Neuroblastoma
Distribution of Metastases at Diagnosis
Data of Dubois et al.

Site	Stage IVS N=81	Stage IV(') NN=133	Stage IV(") N=434
Bone Marrow	34.6%	57.1%	81.3%
Bone	0	48.9	68.2
Lumph Node	8.6	28.6	35.7
Liver	80.2	53.4	12.9
Brain Orbit	0	25.6	19.6
Adrenal	6.2	13.5	6.0
Skin	13.6	8.3	0.9
Pleura	--	4.5	3.7
Lung	--	2.3	4.1
Peritoneum	--	3.8	2.1
CNS	--	0	0.9
Other	--	3.8	1.6

(') patients younger than 1yr, (") older than 1yr

Compared with Stage IV patients, patients with stage IVS had more skin and liver metastases, but a lower frequency of bone and no marrow metastases (Dubois et al.) (table 12.32). Several unusual sites were involved in stage IV patients such as the pituitary, maxillary sinus, parotid gland, lacrimal gland and within the scrotum

They noted at recurrence fewer bone, bone marrow, liver, lymph node and skin metastases than at presentation, but more adrenal, lung and CNS metastases.
The data of the German Cooperative Neuroblastoma trial provide a comparison of the distant metastases between stage IV and stage IVS (table 12.33).

Table 12.33 - Neuroblastoma
Metastatic sites in Stage IV (N=1076)
Data of the German Cooperative Trial (Simon et al.)

Site	IV	IVS
Bone Marrow	84%	47%
Bone	68	none
Liver	18	81
Skin	2	17
Lymph nodes	21	none

About similar data were recently reported by Hero et al. covering 317 patients with metastatic NB of whom 215 with stage IVS.

Neuroblastoma has also been observed in both adolescents and adults. Franks et al. reported on a series of 16 patients. Distant metastases were observed in all usual sites, particular in the breast, the pleura, supraclavicular nodes and the various bones.

The site of the metastases at first relapse were reported by Cotterill et al., from the European Neuroblastoma Study Group, covering 1277 patients. It occurred in 322 patients, of whom 90% during the first year. The sites of relapse are shown in table 12.34.

Table 12.34 - Neuroblastoma
Site of First Relapse
from Data of Cotterill et al. 2000

At Primary Site	45%	Abdominal Nodes	29%
Bone Marrow	57%	Other Nodes	27%
Bone	51%	Pleura	5%
Liver	11%		

Metastases in the CNS

As table 12.32 shows, metastases in the brain are not common, but we have the impression of that they are underreported. Rohrlich et al. discussed 7 cases from their files, while they could retrieve only 30 cases from the literature in 1989. In nearly half, there was an associated leptomeningeal spread. There is apparently no preferred site.
Diffuse leptomeningeal dissemination is a relatively frequent finding at autopsy (DelaMonte et al.). Arterial

Table 12.35 - Comparative Features of CNS Metastases of different Neuroblastic Tumors Modified from DeLaMonte et al.

Feature	NEUROBLASTOMA	MEDULLOBLASTOMA	RETINOBLASTOMA
Origin	Neural Crest (NC)	Neuro-Ectodermal (PNET)	Neural Crest
Regional Distribution	Rostral to Caudal Telencephalon more	Radial from Cerebellum Cerebellum more	Caudal to Rostral More in Lumbar Sac
Structure Involved	Tumor infiltration in Mesodermal (Dura) and NC-derived (Leptomen.) Mesoderm: bone, pancreas Facial bones	In all cases Leptomeningeal Tu with glial differentiation: invasion of white and gray m.	Tumor infiltration in Mesodermal (Dura) and NC-derived (Leptomening) Mesoderm: bone, pancreas Facial bones
Site of metastases	Dura 15/16; LM 6/16 D.Cerebell 3/16; cord 1/16 LM brain stem 1/16 (Dura 94%)	LM cerebellum 70%; LM hemispheres 39% LM diencephalon 26% (Dura 9% = rare)	Telencephalon 8/8; spinal cord 7/8; LM 7/8; subarachn. Stem 5/8; Telencephalon 7/8 (Dura: 63%)

spread with subsequent CSF dissemination is the most probable mechanism. The clinical presentation is relatively variable and will depend of course on the sites involved and the extension. It should be suspected whenever any neurological symptoms appear.
Dural metastases continuous with skin metastases through the suturae have been described by Chirathivat et al.

The literature on CNS involvement shows two different patterns, the intra-parenchymal and the leptomeningeal. The first is considered either as hematogenous in patients with lung involvement, but can also be secondary to meningeal involvement penetrating into the parenchyma. It has been considered rare, though several cases have been reported, reviewed by Shaw et al.
Zimmerman et al. described epidural deposits on CT-images, finding spread into the sutural margins and compressing the major dural venous sinuses.

In general, intracranial metastasis is usually found as a space occupying lesion, eventually clinically manifested by cranial nerve palsy and bone destruction. Metastases can occur in the dura and brain, the latter being more infrequent. Large dural metastases may compress the brain and cause destruction of overlying bone. Any dural involvement is usually seen as a widening of the cranial sutures on plain radiographs.
Reporting on 10 specific cases, Kellie et al. concluded that the CSF pathway is the major route of spread into the CNS. A survey of the literature disclosed that parenchymal involvement was present in 19 patients. Of these, only 8 had leptomeningeal involvement, 7 of the dura and 5 of the skull.

The variability in the various CNS involvement patterns reported is probably due to a dual pattern, as was found by DeLaMonte et al. in their cluster analysis. They concluded that peripheral neuroblastomas are heterogenic in terms of their metastatic potential. The first ones are likely to metastasize to the dura and the others more likely to choose the leptomeninges. In other words, a subset of the peripheral neuroblastomas tends to metastasize to mesoderm-derived structures such as the dura mater, while the other subset is likely to invade 'neural crest' derivatives such as the leptomeninges. Parenchymal extension is likely to occur from invading dural elements.

Spinal cord compression is not uncommon. Punt et al. were able to report on 21 patients encountered over a period of 17 years. Compression was at the cervical level in 1 patient, dorsal in 9, dorsolumbar in 5 and lumbosacral in 6. Extradural tumor was seen in 20 and in one an intradural extramedullary metastasis was observed. In 15 cases, the intraspinal disease was a direct extension of an extra-spinal mass probably the primary as an hourglass or dumb-bell presentation. About half of the patients also had other metastases.
The comparative features of the various different neuroblastic tumors as outlined in the study of DeLaMonte et al. are in table 12.35. They stress the difference in CNS, but also of extraneural metastases.

Ocular Involvement

According to Musarella et al., three major eye signs are observed: proptosis, Horner's syndrome and opsoclonus, all closely related to the site and the stage of the tumor.
Ophthalmic involvement of any kind occurred in their series in 20% and was the presenting sign in 8%. Proptosis is present in half of them, with periorbital ecchymosis, ptosis and swelling of the adjacent frontal or zygomatic bone.
Unilateral Horner's syndrome is less frequent being observed in 3% and was ipsilateral to a cervical or thoracic neuroblastoma.
Nine children or 2% had opsoclonus-myoclonus pre-

senting with 'dancing' eyes, consisting of rapid multi-directional eye movements, myoclonus and truncal ataxia. The disease was localized in all.
In general terms, it seems that true orbital involvement is almost exclusively associated with disseminated disease.
Choroidal metastases have been reported only on rare occasions.
At birth, the diagnosis of an abdominal mass and an abnormality of the iris was noted in a girl. It turned out to be an abdominal (adrenal) neutroblastoma (stage IVS) (Bowns et al.).

Bone Marrow Metastases

The incidence is high, but its extent was difficult to evaluate before the advent of nuclear scintigraphy and later MRI. Examination of the femur enables to distinguish two patterns: the N or nodular type (16%) and the D or diffuse type (84%) (Tanabe et al.). In this series the N type was not accompanied by bone metastases, while all of the D-type well.
It is almost certain that bone marrow metastases are the first step towards bone metastases as they later will invade the bone cortex. The early stage is detected only with MRI, but when bone is invaded, nuclear scintigraphy will become positive.

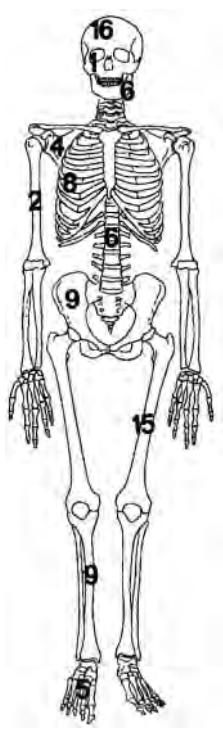

Fig. 12.7- Repartition of the skeletal metastases in 49 patients with neuroblastoma. Drawn from data of Howman-Giles et al.

Bone Metastases

About half of the patients at stage IV will have bone metastases. Data on the distribution over the skeleton are, however, not available. We found a report by Howman-Giles et al. on 49 patients (fig. 12.7) . The most frequently involved site is the skull, and is also the most frequently discussed in the literature.
Metastases to the skull and orbit have been reported in up to 25% of the patients with neuroblastoma. It sometimes preceded the diagnosis of the primary (Egelhoff et al.).
The fact that skull metastases are the most frequent ones has received a certain amount of attention in the literature.
From a radiological point of view, Pascual et al. stressed following points. The diastasis of cranial sutures is generalized and progressive and can reach several centimeters of separation. In the younger child, diastasis is observed at all sutures, while in children older than 4-5 years, it is most common in the frontoparietal sutures.
A significant degree of thickening is frequently observed in the involved calvarian bone with an 'hair-brush' image, mainly located in the frontal region. Bulging is also seen in the cranial vault associated with lacunae. Metastases are also frequent in the orbito-sphenoid region.
Maxillofacial metastases are easily detected by CT or MRI.

Egelhoff et al. have identified four patterns of calvarium involvement: sutural diastasis secondary to dural involvement, rare 'sunburst' appearance parallel with periosteal reaction, lytic defects as direct skull metastases and thickened bone.

David et al. have described different types of metastases in the axial or appendicular skeleton.

1. periosteal reaction,
2. osteolytic focus
3. a lucent horizontal metaphyseal line,
4. vertical linear radiolucent streaks in the metadiaphysis of a long bone,
5. a pathological fracture,
7. vertebral collapse.

Differential diagnosis at presentation with round cell tumors such as Ewings' sarcoma, rhabdo-myosarcoma, leukemia and lymphoma is mandatory.

Gynecological Metastases

We are aware of three case reports concerning ovarian metastases. The case reported by Meyer et al. of a baby of 8 months was bilateral, but apart from the adrenal primary, the abdomen was free. The patient of Mac Hugh et al., a F4, had several abdominal masses and was diagnosed with bilateral ovarian involvement. Six months after first diagnosis, a girl aged 15 presented with increased abdominal girth and mass. At laparotomy, both ovaries were found to be involved (Somjee et al.).
Reviewing the patients treated at their institute, Meyer et al. found ovarian metastases, either surgically or at

autopsy, in 10 of the 21 female patients. Bilateral involvement was present in 7.
Lynn et al. have reported on a congenital neuroblastoma diagnosed at birth and associated with several microscopic placentar metastases. They could retrieve 10 other similar cases between 1964 and 1985 from the literature. Maternal metastaseswere never found.
Silverman et al. mention one case (F13) metastatic to the breast.

Testicular and Paratesticular Metastases

From the files of the German Cooperative Neuroblastoma Trials, Simon et al. were able to report on this particular metastatic site. They found 11 children at presentation or 1% and an additional 4 during presentation. Two children had a tumor per continuitatem. The homo- or heterolater-ality was not studied, but all, except one pelvic and one abdominal were adrenal primaries.
The authors could retrieve 26 other reported patients from the literature. They discussed the pathway of this metastasis in terms of migration of paraganglionic cells during embryonal life, regressing normally within two years of age. Finally, they suppose a lymphatic spread as the primaries were all infra-diaphragmatic. Migration of malignant cells along spermatic vein is not discussed.

Non-Regional Lymph Node Metastases

Metastases in all distant node stations such as the cervical, axillary, mediastinal and inguinal nodes have been reported. Such metastases were reviewed by Yamada et al. who reported on 8 patients with distal node metastases. The primaries were, except for 2 with an unknown primary all abdominal.

Other Metastases

Intrathoracic metastases may manifest themselves as pulmonary nodular infiltrates. The most frequent are, however, bone erosion of ribs and spine. Mediastinal and retrocrural lymphadenopathy are not uncommon.

In a multicenter prospective study on 567 stage IV pediatric patients, CT disclosed pulmonary metastases in 17 or only 3%, confirming the low incidence. They are almost always multiple and of rather small size (table 12.36) (Kammen et al.).

Table 12.36 - Neuroblastoma Stage IV (Ped.) Pathology of Lung Metastases at CT (N=567) Data of Kammen et al.

Number	1-10	11
	11-20	3
	>20	3
Size	0.5-1cm	11
	1.1-2	2
	2.1-	4

Within the abdomen, metastases may involve all abdominal viscera, lymph nodes, the mesentery and the pelvic organs.
Newland et al. have reported on a six-year old boy presenting with unilateral mandibular swelling, osteolytic at further imaging. Although an abdominal problem was suspected, further investigations were only done after a mandibular biopsy had disclosed the diagnosis of neuroblastoma.

Causes of Death

Death will occur by tumor extension, tumor metastases or complications of the extension and of treatment. Hsu et al. observed liver failure, hemoperitoneum, sepsis and inferior vena cava compression to be the most frequent causes together with sepsis, diffuse intravascular coagulation and radiation sequellae.

References

Caution: References are given for documentary purposes. Not all have been reviewed or used in the redaction of the text. We do not claim completeness of data. The references are as much as possible grouped per subject heading. For some headings, only reports after 1974 are listed.

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13
METASTASES from TUMORS of the HEAD and NECK

In oncology the term 'Head and Neck' is applied to the anatomical tissue volume located below the skull base and situated anteriorly to the cervical spine. In the strictest sense according to the oncology literature, it concerns the nasopharynx, the sinonasal complex and the structures enclosing the oral cavity. For convenience and to extend its significance, we include in this chapter tumors of the salivary glands, the orbit and its contents, the thyroid and parathyroid glands cervical paragangliomas and esthesioneuroblastoma.

METASTASES from the MALIGNANT TUMORS of the SALIVARY GLANDS

Spread

Local Evolution

Any tumor within any gland will first grow and then expand. The smaller the involved gland, sooner the tumor will be noticed. After further growth, malignant tumor will invade and expand through the gland capsule, penetrating within the surrounding tissue and structures.

Local invasion is the initial route of spread. Pain and skin adhesion are manifestations of the aggressivity of the tumors and the hallmarks of malignancy. One particular problem concerns the parotid tumors who enclose and invade the facial nerve. This is discussed further.

Regional Lymphatic Metastasis

The metastases in the regional lymph nodes are of considerable importance in the evolution of malignant salivary gland tumors. Histology type will play a major role in the local progression and on prognosis.

Fig.13.1 - Lymph drainage from the major salivary glands: superficial prae-auricular nodes, jugulo-digastric node, deep pre-auricular node, deep intra-glandular lymph nodes

The LYMPH SYSTEM of the SALIVARY GLANDS

The parotid gland has a rich network of lymphatic vessels within its parenchyma and periphery. About 20 to 30 lymph nodes are present within the gland. The afferent lymphatic may pass directly into the intraparotid lymph nodes. Other afferent vessels may circumvent the gland and go directly to the paraglandular nodes. The main group is situated in the pre- and supratragal area. A smaller number of nodes is associated with the lateral, posterior and inferior portions, but none with the deep lobe. The efferent channels from the parenchyma drain into the superior deep jugular chain. They are connected with the spinal accessory, submandibular and superficial lymph node system (fig. 13.1).

MacKean et al. have examined the proportion and location of intraparotid nodes. Virtually all nodes found were superficial to the facial nerve. Within the older age group, less than 1% were in the deep lobe. About 70% were in the lower half of the gland (fig.13.2).

From the capsule of the submandibular gland, the efferent lymph vessels are connected primarily with the deep jugular system and the nodes along the vascular chain.

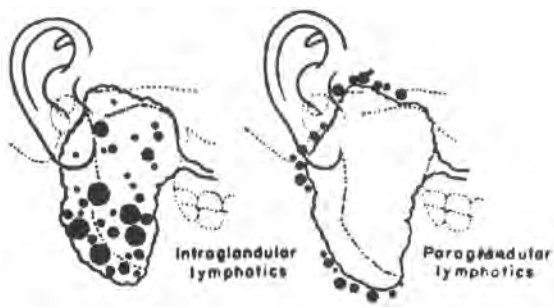

Fig.13. 2 - Parotid Gland tumors - Distribution of lymphoid tissue (Conley and modified by Mac Kean et al., with permission)

The registration of lymph node metastases in the various reports is not always easy to compare. We have tried to select data in reports on well-defined tumor site and eventually the different histology types. Spiro et al. reported interesting data for malignant tumors of the parotid according to histology and method of diagnosis (table 13.1).
The most complete data on cervical nodes from submandibulary malignancies have been provided by Spiro in 1976 (table 13.2).

Table 13. 1 - Malignant Parotid Tumors
Cervical Lymph nodes according to histology type
Data of Spiro et al., N=288 , 1975

Histology	N	At adm.	Occult	Later	Percent +
MucoEpi.LG	56	0	0	0	0
MucoEpi.oG	89	25	10	4	44%
Mal.Mixed	53	5	0	6	21
Acinic Cell	33	2	2	2	18
AdenoCa	28	5	2	3	36
Aden.Cystic	20	1	0	1	10
Squamous	10	1	4	2	70

(LG: low grade; oG: other grades; ad adm.: ad admission)

Table 13. 2 - Submandibular Gland malignancies
Metastases according to histology (N=121)
Data of Spiro 1976

	N	Lymph Node Present	Occult	In FU	Percent Positive
Anapl./Uncl.Ca	3	1	2	0	100%
Epidermoid	15	1	7	1	60%
MucoEpi HG	19	5	6	0	58
Adenocarc	14	2(‘)	5	0	50
Malign.Mixed	23	4	1	0	22
Adenoid Cyst	42	6(‘)	1	2	21
MucoEpi LG	4	0	0	1	0
Acinic cell ca	1	0	0	0	0
All	121	19	22	4	37

(‘) previous excisional biopsy in 1 patient

From the anterior part of the sublingual gland, the lymph drains predominantly to the jugulodigastric and deep jugular nodes (Conley).
There are no data on the incidence of lymph node metastases specifically for this gland. Some authors have provided data according to histology and site. We found data for adenocarcinoma (table 13.3) and for mucoepidermoid carcinoma (table 13.4).

Table 13.3 - Tumors of the Salivary Gland
Lymp Node metastases (N=204)
Data of Spiro, 1982

Site	N	Lymph node initial	later	total (%)
Parotid	58	12	4	16 (28%)
Submandibular	8	4(‘)	0	4 (50%)
Minor gland	138	19(°)	16	35 (25%)
Primary treated	115	24(‘)	12	36 (31%)
Previously treat	89	11(°)	8	19 (21%)
Grade 1(“)	37	1	1	2 (5%)
Grade 2	115	17	11	28 (24%)
Grade 3	45	14	8	22 (49%)

(‘) previously excised in one patient
(°) previously excised in two patients
(“) excludes two ‘ungraded’ patients and six post-operative deaths.

Table 13. 4 - Tumors of the Salivary Gland
Metastases of MucoEpidemoid Carcinoma (N=367)
Data of Spiro 1978

Site	N	Lymph node initial	later	total (%)
Parotid	254	64	6	70 (28%)
Submandibular	23	11	1	12 (52%)
Minor gland	90	13	11	24 (27%)
All	367	88	18	106 (29%)
Primary	215	43	14	57 (27%)
Prev.treated	152	45	4	49 (32%)
Low grade	138	8	4	12 (7%)
Interm.grade	139	33	9	42 (30%)
High grade	82	43	5	48 (59%)
Not graded	8	4	0	4 (50%)
Stage I	89	0	0	1 (1%)
Stage II	50	3	4	7 (14%)
Stage III	69	38	8	46 (67%)

Although the diagnosis of adenocarcinoma is now regarded as obsolete, we thought it worthwhile to include the data of Spiro, since they were so precisely presented. They also allowed to draw some conclusions. Their is obviously a relationship between tumor grade and node frequency, but not according to the primary site.

Metastases in patients with mucoepidermoid carcinoma occurred in about one-third, 24% confirmed at presentation and another 5% during follow-up. The frequency is higher in those from the submandibular gland and as could be expected in high-grade and advanced (Stage III) tumors.

Distant Metastases

The incidence of distant metastases varies according to the histological type, but there is also a time-dependency incidence after the diagnosis. Specific studies on the pattern of metastases are lacking either in terms of function of the primary site or according to histology. In spite of an incidence higher than cervical nodes and of the fact that more than half of the deaths are attributed to distant metsatases, no specific data either clinical or from autopsy studies are available.

Of all salivary gland tumors, the incidence of distant metastases is the highest in the undifferentiated, epidermoid and adenoid cystic carcinoma (table 13.5). Two series are compared. The comparison is difficult, as some histology types presented are no longer valid. The rate of metastasis from mucoepidermoid carcinoma is higher for the submandibular gland than for the other sites (Spiro et al.).
Data should be viewed with caution, as length of follow-up is not considered, or the proportion of advanced patients treated.

Table 13.5 - Major Salivary Gland -Malignant tumors
Incidence of distant metastases by histology

Histology	Tran(1986) N=133	Spiro(1989) N=47
Acinic Cell carcinoma	10%	5%
Epidermoid carcinoma	13	42
Mucoepidermoid carc.	16	23
Malign.Mixed Tu	18	16
Adenocarcinoma	37	26
Adenoid Cystic carc.	41	32
Undifferentiated	43	--
All	26%	19%

A literature review by Shingaki et al. covering 852 patients revealed an overall incidence of distant metastases of 41%. Malignant tumors of the parotid indeed kill more by distant metastases than that they metastasize in the regional nodes. This is especially true for the adenoid cystic carcinoma.

Table 13.6 - Carcinoma of the Parotid gland
Incidence of metastases during follow-up

Histology	Eneroth 1970(“) N=345	Gallo 1997(‘) N=124
Solid undifferentiated	57%	63.6%
Adenoid cystic carcinoma	43	24.0
Carc.in pleomorph. adenoma	43	--
Mucus prod. adenopapill. carcin.	28	--
Acinic cell carcinoma	19	20.0
MucoEpidermoid carcinoma	11	17.2
Epidermoid carcinoma	--	19.0
Adenocarcinoma NOS	--	35.3
Malignant mixed	--	33.3

(“) length of follow-up not stated
(‘) minimum follow-up 5 years

During follow-up, the metastatic rate can be relatively high (table 13.11.24, data of Eneroth). The recent data by Gallo et al. have been added for comparison. The data are comparable, though histology-typing is not consistentt.

Discussing the risk factors for metastases from one site is relatively difficult and in fact not sound, as the histology type is the first determinant. The study of Gallo et al., shows that the overall stage of disease is important, as can be expected. They do not analyze it further according to histology, but state that there is an indication of. The low number of each type probably makes conclusions difficult. Only one report deals specifically with distant metastases from malignant tumors of the submandibular gland (table 13.7).

Table 13. 7 - Cancer of the Submandibular Gland
Frequency of metastases according to histology
Data of Spiro et al.1976, Follow-up min.8 years

Histology	Cerv.lymph Node(°)	Distant
Anapl.Unclass.Carcin.	6/6 (100%)	1/3 (33%)
Epidemoid carcinoma	9/15 (60%)	none
Mucoepidermoid >GrI.	11/19 (58%)	4/19 (21%)
Adenocarcinoma NOS	7/14 (50%)	7/14 (50%)
Malignant mixed tumor	5/23 (22%)	11/23 (48%)
Adenocystic (‘)	8/42 (21%)	24/42 (57%)
Mucoepidermoid GrI.	1/4	none
Acinic Cell carcinoma	0/1	none

(°) ad admission, surgery and during follow-up
(‘) probably adenoid cystic carc.; NOS: not otherwise specified

Table 13. 8 - Carcinoma of the Salivary Gland
Recurrence and Metastatic rate by histology
Data from Yu et al. 1987 (‘)

Histology	Recurrence	Node	Distant
Adenocarcinoma	67.2%	46.6%	6.9%
Adenoid Cystic	47.9%	2.1	34.0
Mal.Mixed	43.9%	12.3	1.8
Squamous cell	(5/9)	(3/9)	(1/9)
Mucoepidermoid	25.8%	10.8	3.3
Acinic Cell	16.7%	0	5.6

(‘) groups with number too small are omitted

A large study of 181 Chinese patients, with 44.7% malignant parotid tumors and 37.2% minor salivary tumors, was reported by Yu et al. (Table 13.9).

Table 13.9 - Carcinoma of the Salivary Glands
Recurrence and Metastatic rate by site
Data from Yu et al. 1987

Site	Recurrence	Node	Distant
Parotid	32.6%	14.9%	7.7%
Submandibular	57.7%	28.9	21.2
Sublingual(‘)	54.5%	28.6	0
Palate	50.0%	11.6	5.8
Retromolar	41.7%	16.7	11.1
Tongue	33.3%	5.6	38.9
Oral mucosa	30.8%	3.8	0
Lip	none	0	7.7

(‘) 21 cases !

Interesting data have been provided on the recurrence

and metastatic rate by histology type (table 13.8) and by site (table 13.9).
The higher incidence of distant metastases with tumors of the submandibular gland and of the tongue is remarkable. According to histology, the well-known propensity for distant metastases of adenoid cystic carcinoma is confirmed (Yu et al.).

According to Histology Type

Reviewing 196 cases of adenoid cystic carcinoma of all sites, Spiro noted distant metastases in 74 patients or 38%. Of these, 23 had only distant metastases without local recurrence, while the lung was involved in 67 (90% of the metastases). It was the only site in 50 patients (table 13.10). They are compared with data from other series.

Table 13.10 - Salivary gland - All sites
Adenoid Cystic Carcinoma - Distant Metastases

	Rountwaite (1977)	Seaver (1979)	Hamper (1990)	Spiro (1997)
follow-up	min.2 yrs	min. 2yrs	min. 3yrs	
Lung	5/18(')	24/93	17/90(°)	67/74(")
Bone	5/18	10	5/90	11
Viscera	0	--	---	5
Brain	3/18	4	7	1
Skin	1/18	1	4	0
Liver	---	3	5	--
Pleura	---	1	2	--
Adrenal	---	--	1	--
Peritoneum	---	2	1	--
Perineural	---	19	--	--
Spleen	---	1	--	--
Stomach	---	1	--	--
Skel.muscle	---	2	--	--

(') all treated cases of minor glands; (") only metastatic cases (°) all treated cases, metastases in 36 patients)

Table 13. 11- Salivary Glands
Adenoid Cystic Carcinoma (N=71)
Frequency of Metastases according to site
Data of Matsuba et al.,1986

Parotid	10/18	56%
Submandibular	7/9	78%
Paranasal Sinus	11/19	58%
Palate	2/9	22%
Other	7/16	44%

The incidence or frequency of metastases according to the primary site of ACC has been reported by Matsuba et al. (table 13.11). The overall frequency is more than 50%.

Table 13. 12 - Adenoid Cystic Carcinoma (All sites)
Development of Distant Metastases

Time	Major Glands	Minor Glands
3 years	4/17 (23.5%)	3/26 (11.5%)
5 years	6/15 (40.0%)	5/23 (21.7%)
10 years	8/13 (61.5%)	13/18 (72.2%)

Other interesting data have been provided by Simpson et al. concerning the development of distant metastases in follow-up time and depending on primary site (table 13.12). There is apparently a higher rate in the first 5 years for the major salivary glands, but after 10 years the incidence rate is the same.
A rare extension mode is that towards the skull base with penetration to the cranial cavity through the foramen ovale. This is in fact perineural spread along the mandibular nerve. It is probably more frequent than usually believed, as Laine et al. could retrieve 3 pa-tients from their files, all of the adenoid cystic type.

Mucoepidermoid carcinomas (all sites) have a somewhat lower propensity for distant metastases. Few data are available in the literature. The large series of Spiro (1939-1968) includes 365 patients (table 13.13).

Table 13. 13 - Salivary Gland - MucoEpidermoid type
Distant metastases according to site (N=365)
Data of Spiro,1978

Parotid gland	39/254	(17%)
Submaxillary	4/23	(25%)
Minor glands	7/90	(8%)
(all)	50/365	(15%)

Data about pleomorph adenoma carcinoma are scanty. Reviewing the literature up to 1987, Collina et al. detected 9 cases of pleomorph adenoma with late metastases, adding two from their own files. The long interval between primary treatment and the presentation of metastases is striking. It concerned bone in 7, lung in 4 cases and liver in 1 case. Distant lymph nodes can also appear lately after first diagnosis.

Table 13.14 - Salivary Gland Adenocarcinoma
Frequency of Cervical Node Metastases (N=204)
according to site (data of Spiro et al.,1982)

Site	At presentation	Incl.follow-up
Parotid	12/58 (21%)	28%
Submandibular	4/8 (50%)	50%
Minor glands	19/138 (14%)	25%
Primary treated	24/115 (21%)	31%
Recurrent	11/89 (12%)	21%
Grade I	1/37 (3%)	5%
Grade 2	17/115 (15%)	24%
Grade 3	14/45 (31%)	49%
All patients	**35/204 (17%)**	**27%**

Although no longer recognized as a separate entity, some authors have classified a number of tumors as adenocarcinoma NOS (not otherwise specified) or difficult to classify, but presenting typical glandular and malignant features.

Data from 204 patients were provided by Spiro et al. In general, the frequency of cervical nodes was about 30% for most sites (table 13.14). Almost 75% were from minor salivary glands, 28% from the parotid gland. Data for distant metastases were not provided.
A number of authors have published a few cases with

metastases from malignant mixed tumor. Wenig et al. were ablle to find in the Registry of the AFIP, 11 patients, (10 parotid gland tumors) with distant metastases (table 13.15). Remarkable is that lymph node recurrences and lung metastases occur early, and those of bone and kidney much later.

Table 13. 15 - Mal. Mixed Tumor of Salivary Glands
Distant Metastases (N=11)
Modified from Wenig et al.1992

Cervical Nodes	after 6, 12 and 18 months
Lung	after 8 and 15 months
Retroperitoneal nodes	at 9 months
Bone(')	after 16, 20, 52 months
Kidney	after 27 and 31 months

(') calvaria, shoulder, humerus, femur, ribs, various vertebrae, sacrum, ilium.

Cutaneous Metastases

Several patients have been reported with skin metastases. Such metastases must be differentiated from metastatic local recurrences along the scar. Nevertheless, a number have presented with skin metastases distant from the neck, as well as over the trunk. An unusual case was reported by Zanca et al. An erysipelas-like inflammation on the right cheek was teleangiectatic metastatic carcinoma of a ductal carcinoma treated one year earlier in a 76-year old woman.

Casesof various histologies metastatic to the scalp are listed on table 13.16

Table 13.16 - Parotid carcinoma
Metastases to the scalp

Giltman '77	M58	Mixed carc	Bone	(??)
Faust 1993	F26	Adenocarc	Node	Reveal
Tok 1995	M62	Adenocarc	Node bone	3yrs
Yen 1997	M60	MucoEpiderm	lung-bone)	Reveal.

Other metastases

Ataxia, dizziness and slurred speech occurred in a man of 69, eight months after surgery. A left frontal metastasis associated with several smaller peripheral lesions was found at CT (Gelber et al.). Kazumoto et al. reported on a patient with multiple brain metastases from an adenoid cystic carcinoma of the parotid and could find only two other cases, of which one from a submandibular gland.

The case reports are in contrast with the large number of patients who are said to have distant metastases in the various different series. There are no autopsy series available in the literature.

A number of unusual locations of metastases have been described in case reports (table 13.17). All histologies are implicated and long intervals, some more than 10 years, are not uncommon.

Table 13. 17 - Tumors of the Salivary Gland
Distant Metastases Case Reports

Parotid gland				
Teears 1976	M22	Und.Aden	Sacrum - spleen	1 yr
Twardzik 1976	M32	Mixed	Lungmultiple	19 yrs
	F60	Ad Cy Ca	Lung multiple	1 yr
Dubois 1977	F19	Und Aden	Bone widespr	1 mo
Magnet 1980	M60	Mixed tu	Bone(')	Reveal
Sciubba 1980	M76	MucoEpi	Bone, abdomen Axilla,	Simult
Katzner 1984	F86	Carcinoma	Femur#	2 yrs
Mess 1986	M58	Adenocarc	Bone Le.foot	6 mo
Lossos 1990	M43	Adenocarc	Endobronch	9 mo
Gelber 1991	M69	Ad Cy Ca	Brain	8 mo
Cherian 1992	F30	Mal.Pleom	Kidney Skin	2 yrs
Horowitz 1993	F25	Epiderm	Kidney	8 mo
Hayes 1994	M62	Ad Cy Ca	Le.ringfinger humerus, lung,	3 yrs brain
Hammoud '96	M50	Ad Cy Ca	Brain Lung	10 yrs
Pinilla 1997	M65	Mixed Ca	Choroid	5 yrs
Brown1998	F48	Ad Cy Ca	Kidney bilat	12 yrs
Kazumoto '98	M60	Ad Cy Ca	Brain	15 mo
Vinette 1999	F61	Sal.Duct Ca	Uterus	3 yrs
Galed 1999	M60	MucoEp	Pleura	2 yrs
Friedrich2000	F61	EMC	Sin.Max.Lung Bone feet	5 yrs
Czader 2000	F54	Mixed	Kidney-Lung	6mo(°)
Submandibular				
Weitzner 1975	M52	Ad Cy Ca	Great toe	6 yrs
Wajed 1978	F56	Mixed Tu	Bone+Extradur	18 yrs
Jenrette 1982	F57	Ad Cy Ca	Choroid	2 mo
Riela 1983	F54	Ad Cy Ca	Bone +extradur	17 yrs
Lee 1997	M32	Ad Cy Ca	Brain	5 yrs
Thomas 1995	F58	Adenocarc	Orbit skin	13 yrs
Sublingual				
Smoller 1992	F58	MucoEpid	Skin flank	6 mo
Oral -Nasal				
Forman 1970	F69	Ad Cy Ca	Liver	Reveal
Saksela 1971	M19	MucoEpid	Skin flank	3 yrs
Vinod 1979	M47	Ad Cy Ca	Brain - Hand	6 yrs
Gutmann 1986	M88	Ad Cy Ca	Choroid	12 yrs
Rypens 1991	M67	Ad Cy Ca	FPPal-Lung	2 yrs
Kawamura '93	M37	no data	Patella tibia	4 yrs
Lacourreye '94	F37	Ad Cy Ca	Sinus Cavern	5 yrs
Tanaka 1995	F62	PLGA	Lungs	18 yrs

(') revealed by hypercalcemia; (°) kidney diagnosed 14mo before primary; FPPal. fossa pterygopalatina; PLGA: polymorphous low-grade adenocarci-noma; EMC: epihelial-myoepithelial carcinoma

The case reported by Tanaka et al. is a very unusual one. They found only one other case reported with metastases in a series of 187 cases by Norberg et al. The patient developed bone and lung metastases 17 years after first surgery.

Reviewing the literature from 1858 (!) to 1961, Thomas et al. found 43 cases of 'mixed tumors' of the salivary glands with distant metastases. The histology can be questioned, as some quoted references clearly indicated 'cylindromas'. Interesting, however, is that 12 cases of 'spine only' metastases, almost all lumbar, were found, from 11 parotid primaries.

Taking into account the two cases reported additionally by the authors, one notices a high incidence of bone metastases. It should be remembered that imaging studies prior to 1961 were not like they are today (table 13.18).

Table 13.18 - Mixed Salivary Gland Tumors
Distant metastases
Literature data from 1858 to 1961 by Thomas et al.

Metast.Site	Primary Site Parotid N=32	Submaxillary N=7	Other(') N=6
Lung	17	6	3
Bone	18	2	1
Pleura	5	2	1
Liver	6	2	1
Meninges	2	1	0
Abd.viscera(°)	3	0	0
Kidney	1	1	1
Other sites	6(")	1(°°)	1(*)

(') sublingual 1; tonsil 1; maxill.antrum 1; cheek 1; palate 1; unknown 1.
(°) not otherwise stated. (") handpalm 1; skin 3; finger 1; gallbladder 1; (°°) adrenal 1; (*) spleen 1.

As mentioned in the different reports, the lungs are a frequent site for distant metastasess. However, data on size, sites, number and incidence are absent, except in the study of Hunter et al. (fig. 13.3). Undifferentiated and adenoid cystic carcinoma are the most frequent primary histologies.

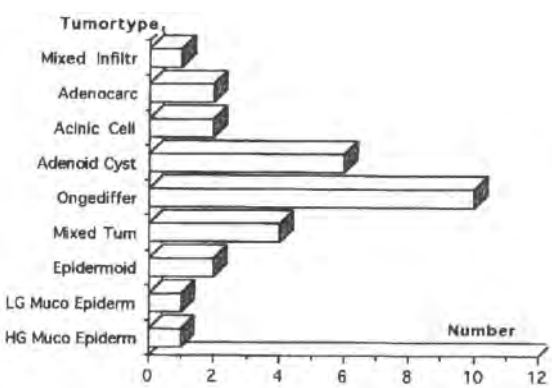

Fig.13.3 - Frequency of Lung metastases depending on histology type in 29 of the 184 patients (110 parotis) with malignant neoplasms of any salivary gland (drawn from the data of Hunter 1983)

METASTASES from CANCER of the NASOPHARYNX

Cancer of the nasopharynx is relatively uncommon in Western countries, but almost epidemic in South China. The extensive knowledge of the locoregional and distant spread is based on the high number of patients in that region.

The large majority are of the epidermoid or squamous cell carcinoma type. A lymphomatous variant is also found. However, a number of authors include aberrant salivary gland tumors and even the rare sarcomas. They certainly have a different behavior.

According to the WHO, the following forms have been identified:
Type I: 'squamous cell' (epidermoid keratinizing), Frequency 30à50%.
Type II: Non-keratinizing;
Type III: Undifferentiated carcinoma.
Types II and III are now divided into:
Category 1: squamous cell tumor
Category 2: undifferentiated UCNT
(Undifferentiated carcinoma of the Nasopharyngeal Type), including the lymphoepithelioma.

Of the head and neck cancers, the nasopharyngeal carcinoma stand out with particular features as a propensity for extensive local spread and a high rate of lymph node metastases. The rate of distant metastases is high compared with the other H&N cancers and has a hgighly variable clinical presentation.

Local Spread

Nasopharyngeal cancer uses many local routes to spread in the immediate vicinity of the cavity to invade several structures and organs, resulting in a highly variable and confusing symptomatology. This leads to the involvement of several medical disciplines in the diagnosis of these tumors but also implicates frequently long delays before diagnosis is established.
The local invasiveness can readily be understood by a good knowledge of the anatomy of the region.

The nasopharynx should be seen as a six-wall irregular cavity. It is located behind the nasal cavity - the choanae - above the pharynx and beyond the palate, and anterior to the two cranial vertebrae and the clivus of the skull base.The Eustachian tube orifice is in the lateral wall, and beneath the fossa of Rosenmuller, probably the commonest site of origin of nasopharyngeal cancer.
At the base of the mucosa, a solid and resistant fascia or pharyngeal aponeurosis is continuous with the fibro-cartilaginous tissue filling the foramen lacerum at the apex of the temporal bone. This zone is however the site least resistant to the penetration of tumors towards the middle cranial fossa, through the foramen lacerum and the foramen ovale. The various cranial nerves should in the first place be seen as 'guides' along which tumoral spread can occur in a 'perineural' fashion, a dreaded situation in the local spread towards the skull cavity (fig. 13.4 & 5).

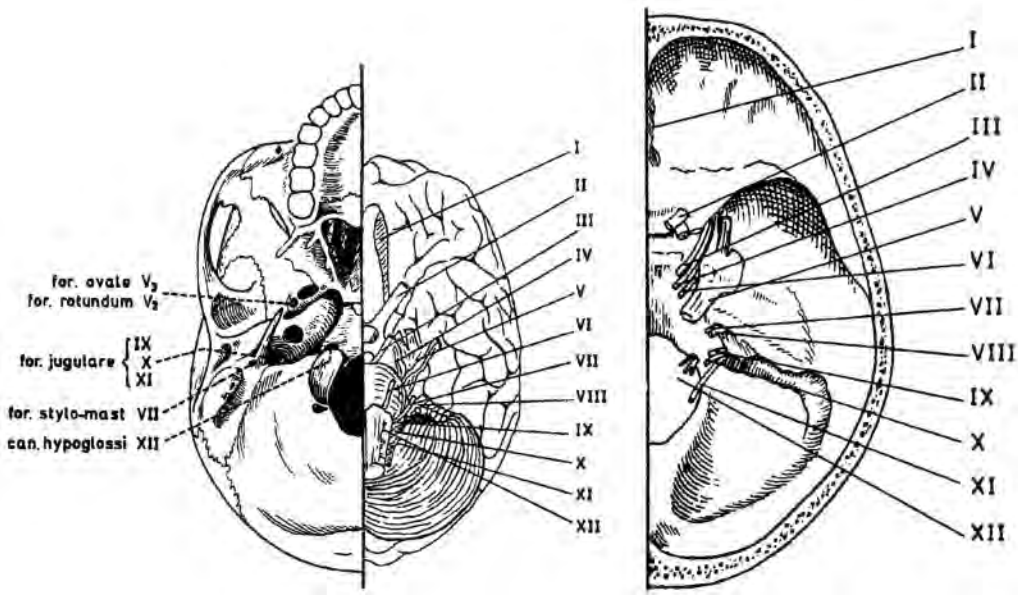

Fig. 13.4 - Anatomy of the Skull Base related to the lower surface of the brain with the foramina and the cranial nerves exit

Canalis Opticus	Nervus Opticus
Foramen Ovale	Trigeminus V3
Foramen Rotundum	Trigeminus V2
Fissura Orbitalis Sup.	Nervus III, IV, VI
Fissura Orbitalis Inf.	Nervus Infra-orbitalis, Nervus Zygomaticus
Foramen Stylomastoideus	Nervus Facialis
Foramen Jugulare	Nervus Glossopharyngicus Nervus Vagus Nervus Accessorius
Canalis Hypoglossus	Nervus Hypoglossus

From the paranasopharyngeal space, the tumors may invade the masticator space, containing the m.temporalis, the m.masseter and the medial and lateral m. pterygoideus.

Various important anatomical structures and cavities lie in the immediate vicinity of the nasopharynx: the occipital bone, the sphenoidal sinus and the fossa infra-temporalis or maxillo-pharyngeal space, located anteriorly to the Eustachian orifice and extending laterally to the vertical ramus of the mandible. The maxillary (V2) and the mandibular (V3) nerves are located within the latter space. Laterally and slightly behind the nasopharynx is the retro-parotid space, containing several cranial nerves (IX, X, XI and XII) are present, as well as the vascular trunk of both carotid arteries and jugular veins and the cervical sympathetic chain.

The involvement or invasion of these spaces and structures gives rise to the likelihood of a wide variety of neurological syndromes at presentation or at recurrences.

Contiguous spread of the nasopharynx may be viewed in several ways (table 13.19).

In the first place, there is spread along the mucosa and submucosa. Spread of the tumor occurs 'finger-like' following muscle bundles, fibro-fatty tissue planes around the muscles, neurovascular bundles then entering skull-bones via the normal foramina and spreading along the periosteal surfaces or along the bone marrow spaces after they have been invaded.

The regions or spaces invaded will depend in the first place on the tumor site within the nasopharynx. Further local extension will add new invasion ways, so that an extensive spread will be observed.

The other way of spread is perineural along the different cranial nerves, frequentlty associated with those previously discussed.

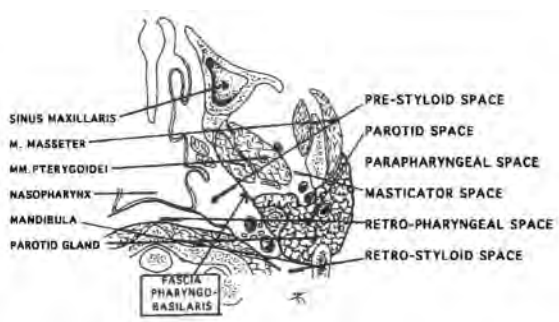

Fig.13.5 - The different spaces around the nasopharynx. The masticator and the parotid sapce are limited by the fascia-pharyngo-basilaris to the pre- and retro-styloid spaces.

An important anatomical structure in the neck, as far as extension is concerned, is the fascia pharyngo-basilaris dividing the lateral neck in a pre- and post-styloid space (fig. 13.5). Its thoughness constitute a barrier, channeling and limiting spread in one of its spaces, although several spaces may be invaded.

As the nasopharyngeal tumors are located in the upper or cranial part of this fascia, it will also 'use' the gaps between the skull base and the upper margin of the fascia to enter the parapharyngeal space. From there it can extend to the skull base, the foramen ovale and the trigeminal nerve V3. It can then extend further to the post-styloid compartment, creeping along the carotid canal to the sinus cavernosus, where several cranial nerves will be disturbed (III, IV, V and VI). Downward, it will follow the carotid-jugular-nerve bundle resulting in the various jugular syndromes (IX-X-XI-XII).

Further spread either at the clivus, the bottom of the sphenoid, or the temporal bone (foramen lacerum) will extend osteolysis and destruction, with invasion of the subdural tissue and possibly the cranial cavity.

Anterior spread towards the nasal cavity is rare.

Table 13. 19 - Cancer of the Nasopharynx
Pathways of spread in the neck and the cranium

Anterior	Nasal Cavity - Palatum
	Erosion of Pterygoid process
	Fossa pterygopalatina,
	Sinus Maxillaris, Etmoidalis
Lateral - Ant.	Fossa pterygomaxillaris
Lat	Processus Styloideus
Lateral	Foramen Lacerum
	Ganglion of Gasser V
	(ant.) nervus oculomotorius
	(post) meatus acoust. intern. VII
	condylus occipitalis (XII)
Posterior Sup.	Sinus Sphenoidalis to sella
	Sinus Cavernosus III IV V VI
	Stenosis of Carotis
	Carotis-Jugul.Nerve bundle
Posterior	Clivus Cervical Spine, Spinal canal,
	Fossa Posterior
Rosenmuller	Parapharyngeal space
Tuba	Otitis - Internal Ear
Foramina	Perineural Spread -Meningitis

Neurology - Perineural Spread

The most commonly involved nerve is the trigeminal. Clinically, pain along one or more branches of the nerve will be reported by the patient, as well as masticatory difficulties. Partial or complete atrophy of the concerned muscles may be found at clinical examination.

A posterolateral extension will infiltrate the lower cranial nerves directly within the carotid space or the jugular foramen (IX, X, XI).

Invasion of the glossopharyngeal nerve is difficult to ascertain clinically as only the m.stylo-pharyngeus is concerned and is difficult to examine (Chong et al.).

Involvement of the n.accessorius is readily observed as the atrophy of M.Sternocleido-mastoideus and M.Trapezius is easily observed, but not easy to visualize by imaging methods.

The n.vagus is involved when atrophy of the pharyngeal muscle is observed as well as dysphonia with paralysis of the vocal cord is noted.

The ophthalmic palsies are more a sequella of the invasion of the sinus cavernosus, skull base or on rare occasions of the orbital apex, than of a perineural spread.

The frequency of the involvement of the different cranial nerves is variabily reported in the literature. All series, however, agree that the n.trigeminus and n.abducens are the most frequently involved. On fig. 13.6 are the data of Skinner et al., from a series of 437 'new' patients, of whom 52 or 12% patients had a palsy at presentation.

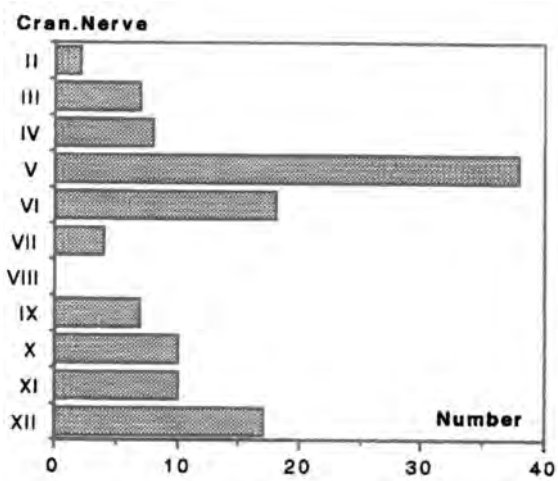

Fig.13.6 - Distribution of cranial nerve involvement in 52 patients from a series of 437 'new patients'. Drawn from data of Skinner et al.

Chong et al. have observed that the involvement of the cavernous sinus does not necessarily implicate cranial palsy. Perineural involvement does not always mean invasion of the neural fibers. This could explain the relatively low incidence of cranial palsy in patients with invasion of the cavernous sinus. They observed infiltration in 29 patients, but only 13 or 45% had palsy of any kind. The small size of the VI may be responsible for the highest frequency of its dysfunction. The maxillary nerve (V2) in the lower part of the cavernous sinus is at the highest risk. This nerve is also at risk, if the sphenoid bone is diffusely infiltrated.

In another report, Chong et al. examined the relationship between the maxillary nerve and of the invasion of the fossa pterygopalatina. This fossa can be infiltrated

1. after invasion of the nasal fossa through the foramen sphenopalatina,
2. erosion and perforation of the pterygoid process,
3. from the masticator space via the pterygo-maxillary fissure.

Via the fossa pterygopalatina, tumors can reach the sinus cavernosus, the gasserian ganglion and the trigeminal nerve (table 13.20).

Imaging

CT and MRI have revolutionized the appreciation of the contiguous infiltration by the nasopharyngeal carcinomas. As most of the cancers are located at the cranial and lateral sites, invasion of the immediately adjacent structures is most frequent. This is very well outlined in the study by Hoe of CT in 56 Chinese patients with histologically confirmed cancers (table 13.20).

Table 13. 20 - Cancer of the Nasopharynx
CT Findings of Contiguous Infiltration (N=56)
Data from Hoe

Involved Space		
Pharyngeal Mucosal		100%
Parapharyngeal space		64%
Loss of normal fatty density	31/56	
Partial obliteration of space	5	
Masticator Space		14%
Infiltration of Infratemoral fossa	6	
Infiltration of Fossa pterygopalatina	2	
Destruction of Pterygoid plate	6	
Involvement of Parotid space		2%
Involvement of Carotid space		23%
Styloid displacement by invasion	5	
Internal Jugular		
Retropharyngeal		38%
Prevertebral space		14%
Intracranial invasion evidence		45%
Opacification of Sphenoid sinus	23	
Infiltration of Sinus Cavernosus	11	
Bony destruction at clivus - base	16	
Inferior Spread		11%
Tonsillar pillar	3	
Anterior spread to Nasal Cavity		2%

A study specifically addressing the infiltrated or eroded bone skull structures was reported by Chong et al. compared the abilities of CT and MRI (table 13.21). The apex of the os temporale, in fact foramen lacerum, is the most frequently involved.

Table 13.21 - Cancer of the Nasopharynx
Skull Base Erosion Observed (N= 114)
Data of Chong et al.

	CT	MRI
Pterygoid plates	9%	7%
Pterygoid process	19	19
Clivus	15	23
Apex Petrosus (For. Lacerum)	18	30
Foramen Ovale	17	25
Sphenoid Body-Sinus	27	28
Sphenoid Wing	11	14

Loco-Regional Spread on Imaging

Involvement of the vidian nerve (nervus canalis pterygoideus) follows the invasion of the foramen lacerum. The nerve courses from the pterygopalatine fossa through the pterygoid canal to the base of the pterygoid process. At CT, erosion of the cortical wall is seen, with enlargement of the pterygoid canal and obliteration of its fat. The absence of bone marrow in this region of the skull base lowers the efficiency of MRI, but the direct demonstration of the neoplastic growth in the canal or at the process allows the diagnosis of perineural spread (Pandolfo et al.).
The vidian canal transmits the vidian artery, a branch of the maxillary artery and the vidian nerve. Perineural infiltration of this nerve will be recognized if the canal is enlarged (Chong et al.). Perividian tumor spread was studied with CT-MRI in 43 patients with nasopharyngeal carcinoma by Blandino et al. Involvement was observed in 6 or 14%. Details about stage were not given.

According to Sham et al., serous otitis media occurs at presentation in 30 to 40% of the patients. Several mechanisms can be invoked for this symptomatology. The first of these is obliteration through invasion of the Eustachian tube, and the second, the neoplastic constriction of the opening through tumor growth. Extension of the tumor in the paranasopharyngeal space seems the most important. Infiltration of the M.Tensor veli palatini, situated just laterally to the pharyngobasilar fascia may result in dysfunction of the Eustachian tube. The infiltration is possible when the tumor has extended beyond the fascia. The authors observed a higher incidence of serous otitis media when the involvement of the paranasopharyngeal space was extensive.

Since most tumors of the nasopharynx are of soft tissue density and are enhanced very little with i.v. contrast, the evaluation of the tumor margin and adjacent involvement is based on indirect signs. These are initial displacement of the paranasopharyngeal space, its subsequent obliteration, obliteration of the hypodense fascial fat planes and asymmetry of the adjacent muscles either from tumor infiltration or neurogenic atrophy (Cheung et al.).

As one would expect, MRI scores better when tumoral soft-tissue is to be visualized than bone destruction such as at the clivus and the respective foramina.
A study by Ng et al. confirmed the statistical superiority of MRI over CT when the following invaded struc-tures had to be evaluated:

M. levator palatini
Carotid space
M. Longus Colli
Skull base
Intracranial penetration
Retropharyngeal nodes

Several other studies concerning the problem have been published. In general, it can be concluded that in fact, both methods are appropriate and complementary.

In a prospective study of 114 patients, Chong et al. observed anterior spread infiltrating the sinus maxillaris in 9%. Associated infiltration of the sphenoidal

sinus occurred in all but one. The invasion of the maxillary sinus is frequently not reported in the series, but usually varies from 4 to 10%.
Of 387 patients with nasopharyngeal cancer, hypoglossal nerve (XII) palsy was present in 21 patients, bilateral in one. It was caused by tumor at first presentation in 4, by tumor recurrence in 2 but due to radiation sequella in 17. This shows that the nerve is involved by tumor at presentation in only 3%, while the nerve is seriously at risk due to the inclusion of the anterior part of the nerve in the radiation field (King et al.).

The recent study by Wakisaka et al. is important. Progress in technology and interpretation of the images obtained with MRI allowed the authors to distinguish 4 different patterns of spread (table 13.22 - fig. 13.7).

Table 13. 22 - Cancer of the Nasopharynx
Pattern of spread observed at MRI
Classification by Wakisaka et al.

Type 1 : Normal situation, mucosal spread only
Type 2 : Tumor on the pharyngeal wall with involvement of adjacent spaces, parapharyngeal lateral and upwards to the skull base:
Type 2a: Unilateral, remaining on one side of the midline
Type 2b : Tumors have extended across the midline
Type 2c : Tumor with upward invasion in the skull base, but not over the midline
Type 3 : Anterior extension, towards the nasal cavity without invasion of adjacent normal structures.

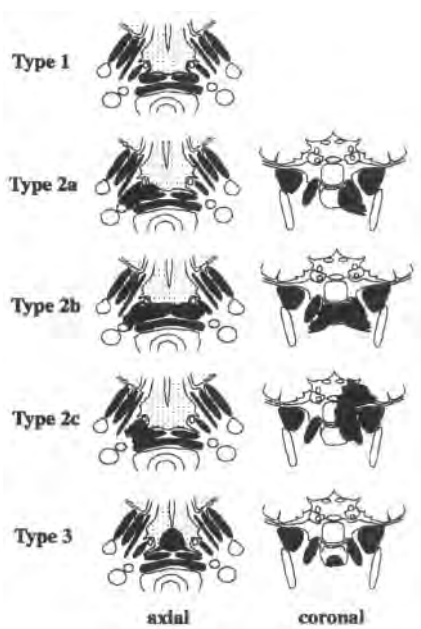

Fig.13.7 - The Classification of tumor spread from a nasopharyngeal carcinoma. The darkly shaded area is the tumor (from Wakisaka et al., with permission).

Table 13. 23 - Cancer of the Nasopharynx
Relation between lymph node and pattern observed at MRI, by Wakisaka et al.

		Cervical		Rouvière	
Pattern	N	Pos.	Neg.	Pos.	Neg.
Type 1	5	5	0	3	2
Type 2a	12	8	4	4	8
Type 2b	3	3	0	1	2
Type 2c	3	0	3	1	2
Type 3	9	9	0	7	2
Total	32	25	7	16	16

An adenopathy located at the lateral retropharyngeal or the node of Rouvière could be observed in half of the patients. In seven it concerned type-3 extension (table 13.23).
As will be discussed further, they found that the distribution of the metastatic lymph nodes depends on the tumor extent. Tumors at the midline present with bilateral nodes, while lateral tumors only have unilateral nodes. They also observed an increased frequency of lymph nodes with increasing tumor volume (data not shown).

Lymph Node Metastases

Nasopharyngeal cancer has a high incidence of lymph node involvement. There is an extensive literature concerning this problem.
The lymphatic drainage goes to the retropharyngeal nodes, the upper internal jugular nodes, the laterally located spinal accessory nodes and the lower jugular and supraclavicular nodes.
In the reports, patients are usually divided into two groups, node negative and node positive, without further specification on metastatic site.
The number of positive nodes at presentation is high, about 75%, the highest incidence of all H&N tumors. Anatomic location within the neck was reported by Sham et al. from 204 node-positive patients from a consecutive series of 271 patients (table 13.24).

Table 13. 24 - Cancer of the Nasopharynx
Clinical Lymph Node Involvement - N=204(°)
Data of Sham et al.

	Right Neck N=134	Left Neck N=150
Subdigastric-Jugular	95.5%	95.3%
Submandibular	14.9	10.7
Upper Spinal Accessory	6.7	10.7
Submental (')	0	0
Mid-jugular	61.9	58.6
Mid-Spinal Accessory	32.8	29.3
Lower Jugular	17.2	14.0
Supraclavicular	10.4	8.0
Lower Spinal Accessory	4.5	4.0
Preauricular	0	0.7

(°) 80 patients had bilateral neck nodes
(') involved submental nodes have been reported in some case reports

This confirms that the highest incidence is at the

upper cervical nodes, particularly at the mandibular angle. The size of these nodes is usually much larger than the size of the other nodes. The nodes at the middle level are rarely involved when the highest level is not involved, demonstrating an orderly mode of involvement. The lower the position in the neck, the lower the frequency of involvement. A consequence of this fact is the poorer prognosis when these lower nodes are involved, as further metastases are out of the treated zone.
The bulk of the drainage goes via the lateral retropharyngeal nodes or the high jugular nodes, from where it continues to the internal jugular and/or the spinal accessory chain.

The relationship between tumor site involvement and the site of the lymph station involved has been addressed by Pfreunder et al. in relation to 80 patients, of whom 59 were node positive. Within the three lymph node chains considered, the most cranial station was always the most frequently involved, confirming the orderly stepwise involvement as described by others (fig. 13.8).

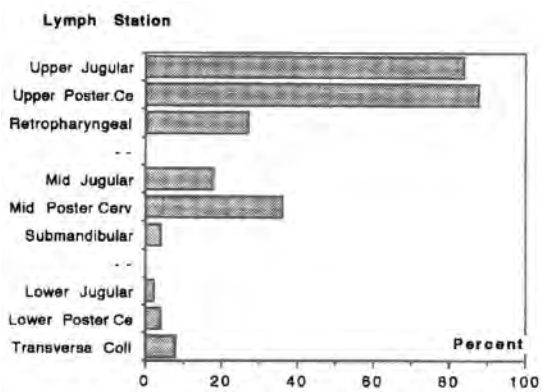

Fig.13.8 - Frequency of involvement of the different neck nodes in 59 node-positive nasopharynx cancer patients. Drawn from the data of Pfreunder et al.

They could also correlate the involvement of each chain with the extent of spread over the mucosa of the nasopharynx. The retropharyngeal nodes were invariably involved whenever the tumor was located or had spread to the posterior surface. The accessory chain is invol-ved in the same situation, though also when the retropharyngeal space was invaded. The tumors situated within the pharyngeal blades of the buccopharyngeal fascia - located at the roof, the anterior and/or the lateral wall - had lymph node metastases in the jugular nodes, with spread within the retrostyloid space. The conclusion is that the site of the primary and the site of extension will determine the lymph node chain involved.
Retropharyngeal nodes were also invaded when the primary has invaded this space. The invasion of the prestyloid space, invariably in the m.pterygoidei, will be associated with jugular nodes and invasion of the retrostyloid space with accessory nodes.

At the lowest level, the lymph drains on the right to the subclavian or jugular vein, while on the left it empties into the arch of the lymph duct or into the subclavian or jugular vein.

In view of the relatively low reliability of clinical palpation, especially in particular neck anatomies, CT will add positive involvement in about 30% of the clinically negative node patients. The nodes in the retropharyngeal space are out of reach for the clinical examinator.

Parotid Invasion

As discussed in Chapter 7, the involvement of the parotid can occur in two ways: In the first place, it will occur via the involvement of the intra-parotid lymph nodes. This is the most frequent form and can occur either from lymphatic spread from the retro- or para-nasopharyngeal nodes, or by retrograde flow from the lower cervical nodes. Two patients presenting with the first mode as first sign were reported by Saw et al.
Involvement through progression from the parapharyngeal space is much less frequent (Chong et al.).

Distant Metastases - Autopsy Data

Reviewing the literature in 1986, Ahmed et al. found an overall rate for distant metastases of 20 to 50% in clinical series and of 40 to 80% of patients at autopsy. In spite of the large number of patients, we found only two reports specifically addressing the pattern of distant metastases, one from the Hong Kong region and one in respect of an American series (table 13.25).

Table 13.25 - Cancer of the Nasopharynx
Distant Metastases - Autopsy Data

Site	Khor (1978) N=352 (“)	Ahmad (1986) N=256
Brain (CNS)	3.3% (°)	no data
Skin	3.3	no data
Lung	30.3	31% (*)
Bone	48.5	48%
Liver	29.3	36%
Soft tissue (‘)	5.5	no data
Nodes below	6.6	43%

(“) length of FU not stated
(°) of the 99 developing metastases
(‘) inclusive muscle
(*) of the 93 patients developing metastases

The three major distant sites are the lungs, the liver and the bones. In a series of 548 treated patients, 90 patients developed distant metastases within a median follow-up time of 18 months. In 70% of these patients bone metastases were found, 47% lung metastases and 50% in the liver. Other metastatic sites as soft-tissue, breast and distant nodes accounted for 16% (Leung et al.).
The metastatic rate (distant) did not differ very much according to histology, except for squamous cell can-

cer in lungs where the incidence was much higher (17% vs 8% for the other, as determined on clinical ground).
After reviewing 180 patients with metastases but without giving precise data, Fandi et al. concluded as follows:
Distant metastases were closely linked to the lymph node involvement. N3-patients had distant metastases in 40%, while more than 90% of the N3 patients died of distant metastases. About 80% of the distant metastases occurred within 18 months after first diagnosis.
Overall, there was no correlation between the size of the primary tumor and the number of metastases.

Thoracal Metastases

Again in spite of the high frequency of metastases (20 to 35% of the patients with metastases), specific studies of the radiological features of pulmonary metastases are rare. Daly et al. have addressed the imaging aspects on chest radiographs in 33 patients and of CT in 8 patients, a low number indeed in view of the large number of patients that could have been studied (table 13.26).

Table 13.26 - Cancer of the Nasopharynx
Radiology of Thoracic Metastases (N=33)
Data of Daly et al. 1993

Hilar- Mediastinal Adenopathy	64%
Idem, alone	36
Idem with multiple parenchymal	27
Multiple Intrapulmonary Metastases	52
Lymphangitis Carcinomatosa	15
Pleural effusion	15 (')
Pleural Mass	3
Endobronchial metastases (")	2 patients

(') in 3/5 bilateral
(") et bronchoscopy

They found a high variability within the radiological aspects, but also that in several instances a number of different metastatic pathologies were seen. A few cases have been reported where the presence of thoracal metastases was associated with hypertrophic pulmonary osteoarthropathy. The latter occurred frequently in the patientsin the study of Fandi et al.
Nozaki et al. have reported on a M42, where a solitary pulmonary metastasis could be resected successfully 15 years after the first treatment.

Metastases to the Central Nervous System

Unlike the above discussed contiguous invasion of the cranial base and dura, true metastases in the brain are rarely reported. The autopsy data quoted above show a low rate of brain metastases. Only a few cases of brain metastases diagnosed during follow-up have been reported (table 13.27).
Cancer of the nasopharynx has apparently some propensity to disseminate within the vertebral canal. A number of cases have been reported involving either intramedullary or extradural metastases (table 13.28).

Table 13.27 - Cancer of the Nasopharynx
Brain Metastases reported

Liaw 1994	M69	Blindness	Bil.Occipital	2 yrs
Zain1994	M56	Dementia	Le.Temp.Pariet	Simult.

One can speculate that the proximity of the nasopharynx to the high cervical vertebrae allows vascular (venous) spread within the vertebral canal, but more reports are needed to permit definite conclusions.

Table 13.28 - Cancer of the Nasopharynx
Metastases in the Vertebral Canal Reported

Morariu 1974	M50	Intramedullar C2-C3	3 yrs
Simpson 1986	M44	Cauda Equina	3 yrs
Elango 1991	M35	Extradural T2-T3	3 mo

Bone Metastases

Metastases to the bone are well known to occur in nasophayngeal cancer, but again data one site distribution are scanty. Tan et al. found an incidence of 17% in 340 patients (table 13.29). The metastases were present at diagnosis in 13 patients.

Table 13.29 - Cancer of the Nasopharynx
Site of Bone Metastases (N58/340)
Data of Tan et al. 1967

Mandible	2	Humerus	4
Spine	44	Sternum	4
Ribs	12	Pelvis	17
Scapula	2	Femur	6

The best data were reported in 1990 by Sham et al. Of 759 patients, 153 or 11.6% developed skeletal metastases. The lesions were lytic in 66%, sclerotic in 21% and mixed in 13%. The median time to diagnosis of bone metastases was 9.5 months, 80% of them developing within 2 years (table 13.30).

Table 13.30 - Cancer of the Nasopharynx
Bone Metastases: Site and time sequence
Data of Sham et al. 1990

Region	First Site N=141	Next site N=80	Total N=141
Skull vault	1.4%	1.4%	3.5%
Humerus	5.0	2.1	9.2
Rib-sternum	7.8	2.8	19.1
Cervical Spine	3.5	0.0	5.0
Dorsal Spine	27.7	12.8	47.5
Lumbar Spine	28.4	20.6	56.7
Sacrum-pelvis	16.3	12.1	39.7
Femur	9.9	5.0	22.7

Typical of a malignancy of the subcranial region, is the fact that the lumbar region is the most frequently involved, 10 times more frequently than the cervical spine and the femur, twice as frequently as the hume-

rus. The plexus of Batson could well be the leading pathway.

Many years ago, Kaplan et al. reported of a solitary metastasis to the shaft of the humerus a few months after the diagnosis of the primary.
The high incidence of vertebral metastases implies a high risk for spinal cord compression after destruction of any vertebra. This is almost never dealt with specifically for nasopharyngeal cancer. In two cases from the series of Tan et al., quadriparesis was the first sign of secundaries in the spine. Leung et al. were able to report on 10 patients, demonstrating that the incidence of that pathology is not low. The 10 patients were from a series of 626 patients treated, or 1.6% within a median follow-up time of 22 months. Of all patients with known skeletal metastases, 13% experienced a spinal cord compression. Contrary to what one would expect in view of the high rate of lumbar involvement, the involved site was located in all patients above T12, with no preferential site.

Bone marrow was examined in 23 patients by Zen et al. and was found positive in 5, or 20% of the patients. These figures demonstrate the high rate of bone marrow involvement, probably underestimated in most series.
In the series of Fandi et al., bone marrow metastases were observed in 23% of the patients with metastases and this correlated with the presence of bone metastases. Chen et al. had an incidence of 19% positive in 41 patients. All BM-positive patients had also bone metastases, while only 38% of the patients with bone metastases had bone marrow metastases.

Other Metastases

In the reported series, the incidence of liver metastases is about 30% of the patients at autopsy. It is remarkable that so few reports are at hand in the literature on distant metastases of this somewhat aggressive cancer.
Hepatic metastases are, as usual, initially silent, but can readily be detected by US-graphy.
One report concerns a rupture of a hepatic metastasis from nasopharyngeal carcinoma in a F46 (Dewar et al.). Obstructive jaundice was the reason for consultation in a M44, where a large liver was found associated with a malignancy at the roof of the nasopharynx. Laparotomy revealed a tumor mass at the porta hepatis compressing the bile duct (Elango et al.).

Metastases to the gastrointestinal tract are not common. They are not mentioned in the autopsy studies. Presenting with an appendicular syndrome 'some time' after treatment of a nasopharyngeal carcinoma, a congested appendix was found at surgery in a man 64 year-old, without other abdominal metastases. One month later, however, liver, peritoneum, mesenterium and several nodes were found to be involved (Hsu et al.).

Cases of cutaneous metastases have been reported over the forehead (Ghaffarian et al.), the scalp, the fore-arm and at the periumbilical region (Yucel et al.); over the thighs, the forearm and the trunk (Jacyket al.).

Penetrating invasion from the sinus cavernosus within the orbit has been reported in some cases.
True choroidal metastases have apparently rarely been reported. Sham et al. reported on a M36 where choroid metastasis occurred associated with pulmonary and liver metastases. Another patient was reported by Ozyar et al.

Two patients with metastases in the breast have been reported by Sham et al. In one patient, metastatic axillary nodes occurred 6 months before the breast nodule was noted, together with several cutaneous metastases over the chest wall.

A most peculiar metastasis was described in a 54 year-old man by Gallerstein et al. presenting with dyspnea. About 3 months after diagnosis of the primary, a large right atrial cardiac mass was noted at echocardiography prolapsing within the tricuspid. Further studies noted a right to left shunt. Surgery could only incompletely resect the metastasis. The patent foramen ovale was closed.

Causes of Death

In spite of the numerous patients treated, apparently no or a minimum of attention has been paid to the causes of death. While about half of the patients seems to be cured at 5 years, quite a number of the patients treated will experience serious sequellae of the treatment, some of them at last lethal.

A report on 99 patients who had died after treatment of a nasopharyngeal cancer has been published by Dawes et al. The report dates back to 1969 however. The whole series concerned 138 patients, but since that time, treatment is certainly more adequate and efficient. About half of the patients died of distant metastases, while a quarter died of local extension of the disease (table 13.31).

Table 13.31 - Cancer of the Nasopharynx
Cause of Death (N=99)
Data of Dawes et al. 1969

Malignant Disease		Other causes	
Local extension	20	Suicide	1
Neck metastases	3	New primary	4
Multiple metastases	37	Bronchopneumonia	3
Lung metastases	5	Peritonitis	1
Cerebral metastases	5	Myocard infarct	3
Liver metastases	5	Cerebrovascular	4
Mediastinal metastases	2		
Toxemia	3		
Exhaustion	3		

Overall Lesson

Nasopharyngeal cancer is an insidious and aggressive cancer hidden in the 'back of the head'. It has the opportunity to invade several strategic and important structures, giving rise to a large variability of symptoms that can mislead the clinician. The overwhelming majority metastasizes in the cervical lymph nodes, while distant metastases are relatively less frequent. The tumor kills more through local invasion.

METASTASES from TUMORS of the HEAD and NECK

Applying the term 'Head and Neck' (H&N) in its commonly used sense, it comprises the tumors of the nasopharynx, the larynx, the sinuses and of the structures surrounding the oral cavity.

Local Spread

The most important feature of H&N cancers is their local destructive invasiveness. The progression within the neighbouring structures will have devastating effects on the local anatomy, with an enormous functional and social impact.
It would seem worthwhile to examine this in relation to a few particular primary sites.

Fig.13.9 - The different routes of extension of a cancer of the floor of the mouth. 1.sublingual gland; 2. intrinsic tongue muscles; 3. tongue; 4. mandible; 5. muscles at the floor.

A meticulous study of the local progression of tumors of the floor of the mouth has been made by Steinhart et al. They identified three different patterns, somewhat modified on fig. 13.9.

Pattern 1 is characterized by invasion of the sublingual gland (93%), the muscles of the tongue (65%) and laterally to the mandible (12%);

Pattern 2 is characterized by a more medial invasion in the space between the tongue and the m. gonioglossus (28%); and

Pattern 3 concerns invasion of the sublingual gland mainly of the lingual musculature (less than 5%).

The rare tumors originating within the frontal sinus may extend either posteriorly and downward to the ethmoid, or perforate the bony wall to the forehead or towards the cranial cavity (fig. 13.10A).
The rare tumors of the sphenoid sinus will extend towards the nasopharynx, possibly invade the upper bony wall to the sella tursica or the clivus to the cranial cavity, or invade anteriorly into the nasal cavity and/or the ethmoidal cells (fig.13.10B).
Ethmoidal cancers can spread towards different structures (fig.13.10 C-D). The first will be the contralateral sinus by transgressing the nasal septum. The antrum and the orbit is invaded after erosion of the ethmoido-maxillary plate. Downwards the nasal cavity can be filled with tumor with invasion of the septum and the turbinates. Up and backwards, the sphenoid sinus will be invaded before the nasopharynx and the skull base, while anteriorly the frontal sinus, the cribriform plate and thus the anterior cranial fossa will be invaded.

The routes of spread of a paranasal (maxillary) sinusal carcinoma depend somewhat on the origin of the tumor.

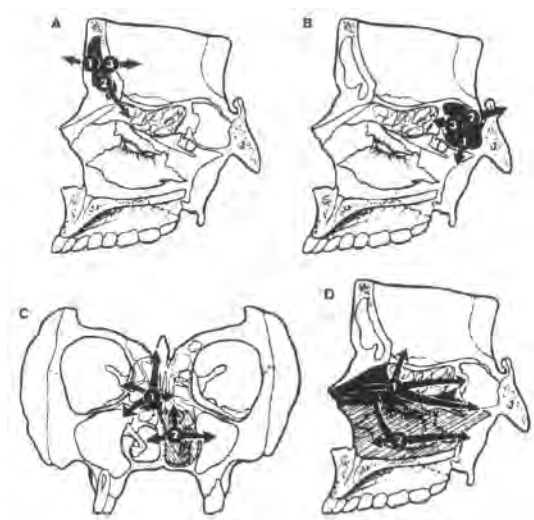

Fig.13.10 - Routes of spread of frontal, sphenoid sinuses and of tumors in the nasal cavity A. from a frontal sinus tumor; B. from a sphenoid sinus tumor; C. from an ethmoidal cancer in the frontal plane; D. in the sagittal plane (from Boone et al. with permission)

The tumors located at the lower part (bottom) of the sinuses, (infrastructure tumors), invade the alveolar process, the gingival sulcus, and medially to the nasal cavity and hard palate. Posteriorly, they will invade

the pterygoid plate and the fossa pterygopalatina.
When they originate at the upper part or the supra-structure, they extent laterally to the zygoma, upwards into the orbit, medially to the nasal cavity and ethmoid, and posteriorly, to the pterygoid plate and the fossa pterygopalatina (fig. 13.11).

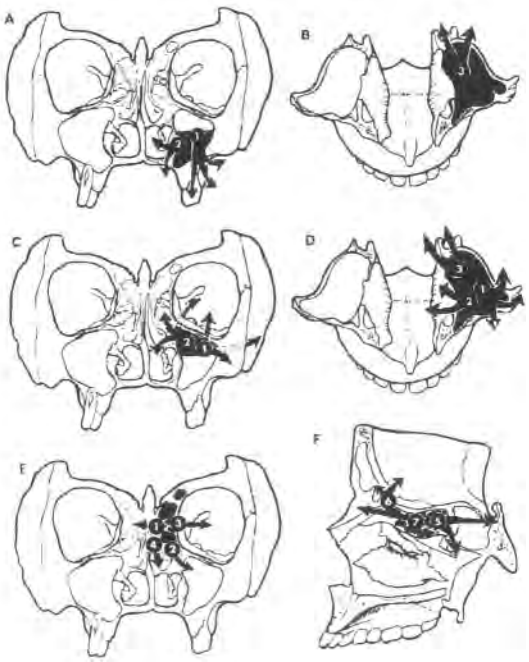

Fig.13.11 - Routes of spread of a paranasal (maxillary carcinoma. A. towards the oral cavity; B. anteriorly to the cheek; C-D. to the orbit and nasal cavity; E-F: spread of an ethmoidomaxillary cancer (From Boone et al., with permission)

The local evolution of paranasal sinusal carcinoma is insidious and the tumor volume reached at presentation may be large. Symptoms will depend on its extent, though more on the invaded structures. In 144 patients diagnosed with paranasal sinus carcinoma, extension to neighbouring structures was seen in 49%, but involvement of two sinuses with extension in 41% (Weber et al.) (table 13.32).

Lymph Node Metastases

It is impossible to completely review the literature on metastatic lymph node metastases in H&N cancers, as the number of reports is infinite. We have taken the liberty of reviewing only the data of Shah, who reported clinical and pathological incidence data in respect of several hundreds of patients (table 13.33). The reader is referred to other publications for more information on the subject.
Clinical examination is of the utmost importance and will separate the NO, clinically-negative neck, from the positive (N1-N3) as first staging. Nodes are also classified anatomically according to the level in neck (fig. 13.12).

Table 13.32 - Paranasal Sinus Carcinoma
Local Extension (N=144)
Data of Weber et al. 1984

Limited to one cavity	5%
Involvement	
of one cavity with extension	49%
of more than one cavity (no extension)	4%
Involvement of one cavity with extension to	
Nasal cavity	41/71
Orbit	28
Oral cavity	21
Pterygopalatine fossa	10
Base of skull - intracranial	8
Nasopharynx	6
Maxillary - zygomatic bone	3
Nasal bone	1
Involvement of more than one cavity with extension to	
Nasal cavity	45/60
Orbit	34
Oral cavity	7
Pterygopalatine fossa	11
Base of skull - intracranial	10
Nasopharynx	6
Maxillary - zygomatic bone	4
Nasal bone	2
Cheek	5

Present imaging methods, be it CT, MRI and FDG-PET scan, have an enormous impact on the detection of node metastases, being much more sensitive than the finger. This will not be discussed further here.

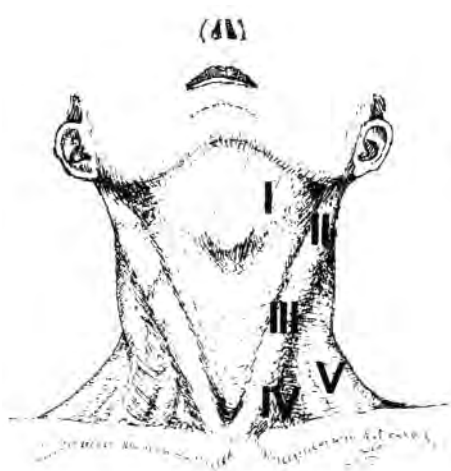

Fig.13.12 - The different neck levels to classify involvement. I: submental region; II: Upper; III: Middle; IV: lower deep jugular node; V: posterior triangle.

The nodes at level III are more frequently involved in the cancers of the oropharynx, hypopharynx and larynx, while level I is more involved in the oral tumors, situated more at the level of the highest neck nodes.

Table 13. 33 - Head and Neck Cancers
Lymph Node Metastases according toPrimary Site
Percentage of positive lymph node metastases
Data of Shah 1990

Clinically Negative NO: elective dissection						
	N	I	II	III	IV	V
Site						
Oral cavity	192	58%	51%	26%	9%	2%
Oropharynx	48	7	80	60	27	7
Hypopharynx	24	0	75	75	0	0
Larynx	79	14	52	55	24	7
Clinically Positive Neck: therapeutic dissection						
	N	I	II	III	IV	V
Oral cavity	324	61%	57%	44%	20%	4%
Oropharynx	165	17	85	50	33	11
Hypopharynx	104	10	78	75	47	11
Larynx	183	8	68	70	35	5

The studies of Pfreunder et al. are most interesting. They correlated spread of oropharyngeal tumors with the incidence of the involved neck nodes. As is well known, the tonsil cancers have the highest incidence of presenting lymph node metastases (Fig. 13.13).

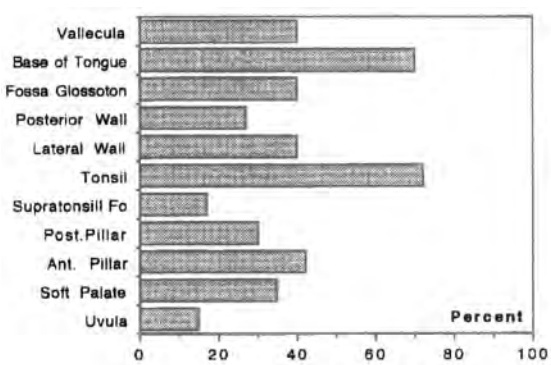

Fig.13.13 - Frequency of Lymph node involvement at presentation of 143 different oropharyngeal cancers. Drawn from data of Pfreunder et al.

They stress the fact that the oropharyngeal tumors originating between the second and third branchial cleft, usually drain to the jugular chain. Of the 143 patients, 102 had a lymph node metastasis, but 80 or 80% of the node-positive only had lymph node metastases within the jugular chain.

After the tumor has transgressed the boundary of the branchial cleft anteriorly, as passing the papillae circumvallatae, the floor of the mouth and the trigonum retromolare, submandibular nodes are involved. The involvement of the lateral or posterior wall of the pharynx and transgressing the posterior boundary, the retropharyngeal nodes are invariably involved. Finally, the spread to the posterior wall and the retropharyngeal space will lead to the involvement of the accessory chain.

Lymph node metastases from maxillary sinus cancers are rarely dealt with in the literature. Only recently, Le et al. reported on 97 patients, where at diagnosis 11.3% presented with lymph node metastases, mainly at level II.

Distant Metastases

There is an enormous literature on the tumors of the Head and Neck as far as diagnosis of the primary and the lymph nodes, prognosis and treatment is concerned. However, having scanned many hundreds of articles on the subject, we found that relatively few authors paid any attention to distant metastases. Several merely quote global number, without specifying sites or incidence data.
Almost all patients will have a squamous cell carcinoma of the mucosa of any site within the H&N. Some authors, however, include lymphoepitheliomas as from the nasopharynx or 'aberrant' salivary gland tumors, changing the homogeneity of the group studied.

Before discussing the distant metastases, it is worthwhile remembering that a second primary is found in up to 10 to 20% of the patients with H&N cancer, posing an important differential diagnostic problem. This topic will not be discussed here, as it is beyond the scope of the book.

Taking H&N-patients as a whole, only about 15 publications contain more or less adequate and relevant data.
In 1951, Peltier et al. reported on the records of 201 patients who had died of a H&N cancer. They noted an incidence of distant metastases of 17%, totalling 65 sites or 1.9 per patient. The lungs and liver were the most frequently involved, but they mention 8 patients with cardiac metastases as the third site, a greater number than in the adrenal (7) and bones (5).
Without specifying the total number of patients, Hoye et al. reported on 22 patients with H&N cancers who died with distant metastases. The lung was involved in all patients, while the other sites varied somewhat (fig.13.14).

In the series of Rubenfeld et al., dating from 1965 and long before the CT era, no sinusal cancers were included, probably reflecting a referral bias. Nevertheless, one notices that the nasopharynx as well as the tonsil, the alveolar ridge and the floor of the mouth have a high rate of distant metastases. The majority of the metastases were pulmonary; 16 of the 28 cases or 57% of the metastases registered. A few bone and other metastases were seen, but the diagnostic possibilities were at that time not what they presently are. The incidence value of 21% is nevertheless indicative.

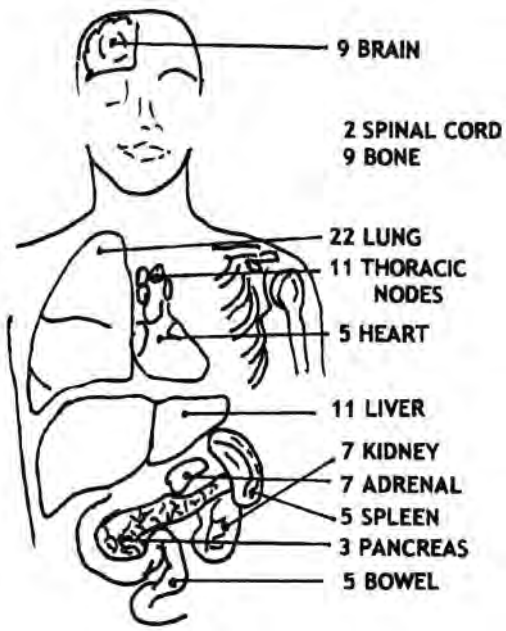

Fig.13.14 - Site of Distant Metastases in 22 H&N-patients dying of disease (Drawn from data of Hoye et al.)

Table 13. 34 - Cancer of the Head and Neck
Site of Distant Metastases (N=279)
Clinical and Autopsy Data of Probert et al.

SupraDiaphragmatic		Abdomen	
Pulmonary	62	Liver	23
Brain	12	Adrenal	8
Heart	7	Kidney	6
Mediastinum	5	Peritoneum	5
Esophagus	4	Spleen	3
Thyroid	2	Prostate	1
Middle ear	1		
Other			
Bone	24	Skin	13
Soft tissue	5	Bone marrow	3

Reviewing the charts of 779 patients with H&N tumors, Probert et al. found a total of 12.3% patients with distant metastases. The incidence was the highest in the nasopharynx group (22.1%), while it amounted 11 to 14% in the other groups, with the exception of 1.4% for glottic tumors. The mean number of metastases per patient was also 1.9. The site of the distant metastases are shown in table 13.34. Slightly less than half of the metastases were detected only at autopsy.
As far as the sites of the bone metastases is concerned, about half were above and half below the diaphragm. With the exception of two femoral metastases, all were in the axial skeleton.

Merino et al. from the MDAnderson Hospital in Houston, reported on a series of 5,019 patients, of whom 546 developed distant metastases, or only 10.9%. The lower incidence than in previous series could be a result of more adequate treatment. Their data are also on table 13.35.

Table 13.35 - Cancer of the Head and Neck
Distant Metastases - Clinical Data

	Rubenfeld N=132 (1965)	Merino N=5019 (1977)
Primary		
Nasopharynx	39%(')	28.1%
Antrum	28%	---
Paranasal Sinus	---	9.1
Alveolar Ridge	33	---
Oral Cavity(")	---	7.5
Floor of Mouth	35	---
Palate	20	---
Tongue	4	---
Tonsil	36	---
Faucial arch	---	6.7
Epiglottis	0	---
Larynx	12	7.3
Pharynx	25	23.6
Sinus Piriformis	20	---
TOTAL	21%	10.9%

(') percentage of patients treated for that specific site
(") includes tonsil, tongue base, pharyngeal wall

They found that about half of the distant metastases were detected within 9 months, and 80% within two years. This is somewhat later than for the locoregional recurrences.
Data on the first metastatic sites according to primary have also been reported (table 13.36). There were 40 instances where multiple metastases were observed at first presentation.

Table 13.36 - Cancer of the Head and Neck
Distant Metastases according to Primary Site
(N=1324 patients with metastases)
Data of Merino et al.

	First Site of Metastases				
Primary	Lung	Bone	Liver	Mediast	Other
Oral Cavity	62	20	1	3	14
Faucial Arch	19	6	2	--	4
Oropharynx	62	17	13	1	5
Nasopharynx	15	34	3	2	7
Sinuses	8	4	--	2	2
Supraglottic	42	10	6	2	7
Vocal Cord	16	1	1	5	5
Hypopharynx	60	19	19	8	8
All	284	111	33	16	52

As first site of metastasis, lungs were the most frequent site, 52% of the metastatic sites. Skeletal metastases accounted for 20.3%, while the other sites each accounted for less than 5%. Bone however was the most frequent first site of metastasis in nasopharynx patients (54%), while liver was the first manifestation in tonsillar cancers (22%) and in base of the tongue cancers (11%).

As can be expected, the number of distant metastases correlates both with T-extent and Stage (table 13.37).

The data must however be interpreted in function of the different primaries included in the different series.

Table 13.37 - Cancer of the Head and Neck
Distant Metastases and Stage (N=1324)
Data of Merino et al.

T1	2.0%	Stage I	5.2%
T2	5.7	Stage II	9.6
T3	8.5	Stage III	12.7
T4	19.5	Stage IV	16.1

Table 13.38 - Cancer of the Head and Neck
Distant Metastases and Stage (N=243)
Data of Berger et al.

Node Status	D.M.	T	D.M.
N0	9%		
N1	17%	T1	25%
N2A	26	T2	20
N2B	23	T3	23
N3A	38	T4	30
N3B	33		
All	23.8%		

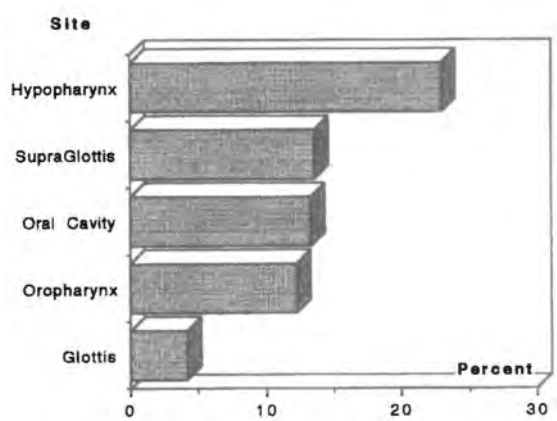

Fig.13.15 - Incidence of distant metastases in 1085 H&N cancer patients, according to primary site. Redrawn from data of Jäckel et al.

Limiting the study to 243 patients treated at the same institution for tonsillar, tongue base and nasopharynx cancers, all tumors with relatively the highest metastatic rates, Berger et al. noted a correlation with nodal status at presentation, but found no difference according to T-extent for this tumor-group (table 13.38). The presence of lymph node metastases is apparently the most important risk factor for distant metastases.

Data from a large series of 1,087 patients, excluding sinonasal and nasopharyngeal cancers, were reported by Jäckel et al. After a minimum follow-up of 2 years, 12% of the patients developed distant metastases.
They found a clear correlation with site - the highest number being in the hypopharynx, and with stage (table 13.39 &fig.13.15).

Table 13.39- Cancers of the Upper Aerodigestive tract
Distant Metastases depending on Stage(N=1085)
Modified data of Jäckel et al. 1999

	N	%DM	LN	N	%DM
Stage I	205	3.4%	N0	609	5.3
Stage II	230	1.7%	N1	139	15.8
Stage III	189	14.3%	N2	254	19.7
Stage IV	463	19.9%	N3	85	30.6

The frequency of distant metastases correlates well wiith stage, which also correlates with the N-status. The T-status had in their series about no influence, T3-T4 patients having an incidence both of 16%, the double of the T2-group.

Other series have been published, but unfortunately they give combined data for larynx and hypopharynx. As both sites have a quite different rate, data are not reliable (Traserra et al.; LeRoux Robert; Alonso).

A number of authors have presented autopsy data.
In 206 autopsied patients, containing only non-nasopharyngeal tumors, Brugère et al. found metastases in only 75, or 36% of the patients. Excluding the patients experiencing postoperative death, the incidence rises to 39%, a quite high number. In 26 of the 75 patients only one metastasis was found (table 13.40)

Table 13.40 - Cancer of the Head and Neck
Distant Metastases - Autopsy Data

	Brugère et al. 1972 N=206		Lerinck 1976 N=144 (°)
	All	Single	
Nodes Mediast.	30	1	6
Nodes Abdom.	10	--	--
Nodes other(')	1	--	--
Lung	58	16	28 (20%)
Pleura	1	1	--
Thyroid	4	4	20 (14%)
Heart	30	--	6
Diaphragm	2	2	1
Stomach	1	1	1
Liver	28	--	18 (12%)
Kidney	15	--	6
Adrenal	18	--	11
Bone	24	1	17
Subcutaneous	3	--	--

(')mamm.int. ;(°) see text

The data provided by Brugère et al. are remarkable in some ways. While thehigh number of pleuro-pulmonary metastases parallels that in all series, the percentage of infradiaphrag-matic parenchymal metastases (39 of the 75 or 52%), was much higher. The number of nodal metastases (77)also represent a higher number than in other series.
Cardiac metastases, mainly pericardial or in the myocard were observed in 18 patients, adrenal metastases in 18 as well, of which 8 bilaterally and renal metastases in 15 patients, of which 12 bilaterally.
Lerinck et al. have also reported precise data from an autopsy study on 144 patients. A number of data are

in table 13.38. Additionally, they mention metastases in the salivary glands, the brain, the esophagus, the pancreas, intestine, spleen and the peritoneum, demonstrating that all organs can be involved.

The data of Papac et al. are cited regularly are, but their number of patients is quite low. The high number of metastases in the larynx group, with 17 metastatic of the 29 treated, is questionable.

Reporting on 832 autopsied patients with H&N cancers, Kotwall et al. observed distant metastases in 387 or 46%, a very high incidence. The majority of the patients had been treated for hypopharynx and base of tongue cancers, but in none of the treated sites was the metastatic rate lower than 32%, even amounting to 60% in hypopharyngeal cancers (table 13.41). A total of 1,250 metastases were found, of which 435 or 35% below the diaphragm.

An important feature of the study is the high number of mediastinal nodes. It would appear that nodal invasion of the mediastinum takes a form of an orderly progression from the cervical nodes on, and can be considered a pitfall for cervical lymph node dissection.

Table 13.41 - Cancer of the Head and Neck
Distant Metastases - Autopsy Data of Kotwall et al.

Above Diaphragm		Below Diaphragm	
Brain	3%(')	Liver	31%
Dura	4	Abdominal Nodes	20
Pituitary	3	Kidney	15
Lung	80	Adrenal	15
Mediast.Nodes	34	Spleen	9
Pleura	15	Small bowel	4
Heart	12	Stomach	3
Pericardium	39	Peritoneum	3
Axillary Nodes	6	Mesentery	2
		Gallbladder	1
Bone	30	Genito-Urinary	1
Soft tissue	8	Colon	1

(') of the 387 patients with metastases

The influence of the node status has already been mentioned above. Ellis et al. have reviewed 455 patients with a minimum follow-up of 2 years. They divided the patients with node groups according to the level of involvement, either above or below the thyroid notch. From their data, the location of positive nodes in the lower neck clearly has an unfavorable influence on the rate of distant metastases (table 13.42).

The same trend was observed in patients who remained disease-free above the clavicle. The authors confirmed that the T stage did not influence the metastatic rate.

The number of metastases at presentation was reported by Bouquot et al. Microscopically proven metastases were observed in 2.7% of the 292 patients. The series did not contain nasopharyngeal cancers though included 83 cases of lip cancer, well known for its low rate of distant metastases and 24 major salivary glands, usually not included in H&N series, and imposing a significant bias on the overall data. They noted an 8% incidence of metastases in nasal and paranasal cancers.

Table 13.42 - Cancer of the Head and Neck
Nodal Involvement and Distant Metastases (N=455)
Data of Ellis et al.

N-Stage	Upper Neck	Upper+Low
N1	10%	22%
N2A	16	50
N2B	19	15
N3A	39	56
N3B	14	27

Other authors have reported some data, but theyadd nothing new. The overall lesson is that distant metastases are more frequent than is usually thought. Several will not be detected, as they will be asymptomatic or will be masked by the locoregional recurrence problem.

Non-Regional Lymph Node Metastases

We have already pointed out that the incidence of mediastinal lymph node metastases is a logical consequence of the involvement of the cervical nodes. The tables on distant metastases also show the occurrence of abdominal nodes, as well as of axillary nodes. Some authors have even found inguinal nodes in a few patients, although a second primary has to be excluded.

Presternal, axillary and inguinal nodes were reported in 5 patients presented by Alavi et al. Three of them were floor of the mouth cancers, one was from the base of the tongue and one from an infratemporal cancer NOS.

Chest X-ray Screening in H&N Cancer

The likelihood of a second pulmonary tumor and/or lung metastases in patients with H&N cancer during foolo-wup is well known.

Table 13.43 - Head and Neck Cancer
Chest X-ray or CT screening Results

Author	N	Results
Houghton 1998	81 patients	14 pulmonary lesions no detail P or Meta
Houghton 1998	111'operable'	Chest CT : 17 lesions 10 malignant lesions 6 multiple = metastases 4 single lesions: n.d.
Nilssen 1999	103	Chest X-ray: 2 synchron.tumors no evidence of meta
Tan 1999	20(III-IV)	all negative
Ong 1999	138	CT+ at diagnosis 12.1% CT+ at follow-up 35%
DeBree 2000	101 advanced Lung	M: 12, Bone M.4

Screening radiology of the lungs at diagnosis is certainly important to a simultaneous lung problem is at presentation. It would, however, appear that, according to the recent data, the yield is very low (table 13.43). As the second cancer or the metastases are not present or not detectable at first diagnosis, the screening results is likely to be very low. This is in accordance with the overall low yield of chest X-ray studies, although its importance should not be underestimated.

Bone Metastases from Head and Neck Cancers

As usual, data on the most common metastatic sites are almost non-existant. This is also the case for bone metastases in spite of their high incidence. We found a few data on the distribution within the skeleton. The involved primaries have, however, not always the same distribution in the previous patient series (table 13.44). As always, there is no uniformity in reporting. About half of the metastases are above the diaphragm. Data on repartition within the spine are non-existant.

Table 13.44 - Cancer of the Head and Neck
Bone Metastases in some reported series

	Bouvier 1972	Arlen 1974	Calhoun 1994
Bone Site	N= 175(‘)	N=116(“)	N=26(°)
Skull	26	2	4
Humerus	17	8	--
Sternum	10	---	--
Clavicle	6	4	6
Scapula	3	3	2
Ribs	30	19	7
Spine	87	44	8
Pelvis	40	---	1
Sacrum-Ilium	---	10	--
Pubis	---	5	---
Femur	17	20	6
Tibia	---	1	---
‘Peripheral bone	14	---	---

(‘) Literature 165 + 10 personal cases
(“) total number of patients with bone metastases not stated
(°) 31.1% had bone metastases

Reporting on 5 cases, Pietropaoli et al. pointed to an incidence of bone metastases of 2 to 4% in patients with H&N cancers. They stress that at radiology, the bone deposits are typically osteolytic with permeative borders. Quite a number are asymptomatic and detected fortuitously.

METASTASES from CANCER of the LARYNX

As the larynx contains three anatomic levels, the supraglottis, the glottis or vocal cord level and the subglottis should be discussed separately.
Cancers of the first anatomical region have the highest propensity to develop nodal and distant metastasis. Cancers of the vocal cord and of the subglottis have a low rate.
As with many cancers, locoregional spread has been more intensively studied than the distant metastases.

Local Spread

Any tumor within the larynx will progress locally along the mucosa, infiltrate the depth and follow the anatomical boundaries and spaces between the different muscular and cartilagenous structures, first within the larynx proper, later alos outside the larynx.
The course will be different for the three different regions, supraglottis, glottis and subglottis.

Supraglottis Tumors

Cancer originating in any part of the region will spread into the entire volume without invading the area below the ventricle. The probable reasons are an embryological, as the supraglottic region develops from the buccopharyngeal anlage and the lower part, the glottis and tracheal from the tracheo-pulmonary anlage. There is, however, no identifiable barrier limiting the downward spread of supraglottic cancers. The supraglottic cancers spread in a cranial or horizontal fashion.
Cancers of the infrahyoid portion of the epiglottis tend to spread anteriorly into the pre-epiglottic space, after having passed the epiglottic perichondrium and the thyro-epiglottic ligament.
Other authors, however, like Weinstein et al., have demonstrated that any vocal cord abnormality in supraglottic tumors may be due to tumorous spread along the mucosa in the vocal cord. They claim that the true incidence of glottic level invasion from supraglottic tumors is at least 20%. This depends, however, on the stage at diagnosis.

Glottic Tumors

Initially, a mobile glottic cancer will be impeded by the tough elastic tissue membrane, the conus elasticus, vocal ligament and its extension into the floor of the ventricle, the thyroglottic ligament. Horizontal spread may cross the anterior commissure to the opposite cord. The dense fibro-elastic tissue at the anterior attachment of the true cords, is the confluence of vocal ligament, the thyroepiglottic ligament, the conus elasticus and the internal perichondrium of the thyroid ala. This is a dense barrier to further spread. Only when there is involvement of the base of the epiglottis can invasion of the larynx framework be observed. More evolved fixed cord cancers (T3) will invade the paraglottic space and the thyroarytenoid muscles. This can occur either by direct invasion of the conus elasticus or lateral spread along the superior surface of the vocal cord.

The spread within the paraglottic space is guided by the conus elasticus medially and laterally by the peri-

chondrium of the thyroid ala. The growth is then directed downwards and laterally between the thyroid and the cricoid cartilage, and through the cricothyroid membrane.
The thyroid cartilage offers resistance to further invasion, but will eventually succumb to a large volume particularly in its ossified parts (Kirchner et al.). The various different directions of spread are indicated in figure 13.16.

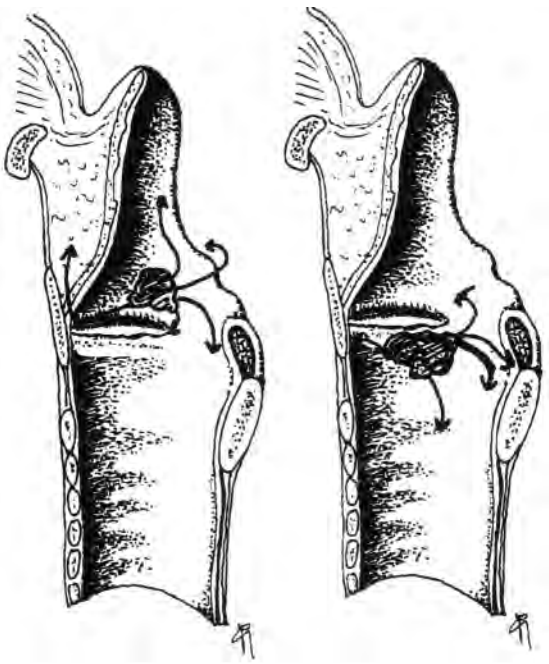

Fig.13.16 - Different modalities of spread of a laryngeal cancer. At the left: a supraglottic tumor, at the right a subglottis tumor

Only recently, data on extension according to the site of the primary were published by Buckley et al. They reviewed 80 laryngectomy-specimens on horizontal sections. Three spaces were considered, the pre-epiglottic (PES), the supraventricular paraglottic space (SPGS) and the infra-ventricular paraglottic space (IPGS).

Table 13. 45 - Cancer of the Larynx
Pathology of Intra-Laryngeal Spread (N=80)
Modified from data of Buckley et al., 2000

		Space or structure invaded					
	N	P	S	I	T	C	CS
Epiglottis	5	2	-	-	0	-	-
Epigl.+ Lat.Supraglott	12	10	7	4	3	0	2
Lateral Supraglottic	12	0	6	3	2	1	2
Glottis only	11	0	0	3	0	0	0
Glottis + ventricle	10	1	5	5	1	0	0
Glottis + arytenoid	4	1	2	4	1	0	1
Glottis + infraglottis	12	1	6	12	5	4	6
Multiregional	14	13	14	13	7	4	6

N: number; P: pre-egiglottic space; S: Supraventricular paraglottic space; I: Infra-ventricular paraglottic space; T: Thyroid cartilage; C: Cricoid cartilage; CS: Cricoid space

The PES was infiltrated in 28 cases, 23 of which concerned an epiglottic tumor. The SPGS was infiltrated in 42 cases, all associated with tumors involving the lateral supraglottis or the ventricle. Invasion of the IPGS occurred in 44 cases and was found in association with glottic cancers (37), extension to the pyriform sinus in 5 and of the ventricle in 3 (table 13. 45). Invasion of PES and SPGS occurs only with extended mucosal lesions, as the supraglottic lesions do not invade the glottic region or IPGS, unless they have extended to the laryngeal ventricle or apex of the pyriform sinus. IPGS and/or the laryngeal framework is not invaded unless tumors of the glottic region extend beyond the vocal cord either laterally or anteriorly. IPGS is thus frequently associated in cords with impaired motility with ventricular, arytenoid or subglottic extension (Buckley et al.).

Extralaryngeal Spread

Extralaryngeal spread where the tumor has reached the boundaries of the laryngeal framework has extensively been studied by Lam et al. It can occur in two directions, either anteriorly or posteriorly.
Tumors invading the laryngeal surface of the epiglottis will invariably reach the pre-epiglottic space. From there it can reach the hyoid bone, the thyroid-hyoid membrane and the thyroid cartilage. From the anterior commissure, it will finally reach the cartilage, while subglottic tumor will infiltrate the crico-thyroid membrane. The cartilage is usually invaded anteriorly at the angle. The thyroid gland is then easily invaded. The space between the thyroid and cricoid cartilage is closed by the crico-thyroid membrane but regularly invaded either by supraglottic tumors coming down or by subglottic cancers.
After growing posteriorly in the para-epiglottic space, the tumor will reach the posterior border of the thyroid cartilage. From this space it will invade the mucosa of the pyriform sinus and eventually ulcerate. From there, it can move to the arytenoids, the posterior cricoid, and move over the upper border of the cricoid to the pharyngeal mucosa.
In a study of 35 specimens of relatively advanced cases, anterior spread at any site was observed in 66%, the cricothyroid membrane and the thyroid cartilage were the most frequently involved, each 19%. Posteriorly any site was involved in 54%, with the posterior border of the cartilage as most frequent. Overall, spread in any direction was observed in 74% of the 35 patients.

Regional (Cervical) Lymphatic Spread

The lymphatic system of the larynx has three major divisions. In the cranial part, lymph vessels perforate the thyrohyoid membrane and join the middle and upper deep jugular nodes. The caudal channels extend laterally through the cricotracheal membrane and drain to the inferior deep cervical and paratracheal nodes. There is also a small anterior drainage path piercing

the crico-thyroid membrane and draining to the prelaryngeal or Delphian node. The latter node mainly receives lymph flow from the thyroid (Olsen et al). It is located in the fascia over the thyroid isthmus, between the cricoid and thyroid cartilage.

Several authors have reported on the nodal metastases from laryngeal cancer, but only a few have reported adequate systematized data according to level of involvement. The data of Candela et al. seem to be very representative (table 13.46). They concerned 247 patients submitted either to elective dissection in a clinical N0-status, or for immediate dissection because of positive nodes at presentation or a dissection necessary in a N0-staged, but presenting later with a neck recurrence (table 13.46).

Table 13.46 - Cancer of the Larynx
Lymph node involvement according to Neck level
Modified from data of Candela et al.

Supra-Glottic	Nodal Level					
	N	I	II	III	IV	V
Elective	65	6%	18%	18%	9%	1.5%
Immediate	119	5	62	53	31	6
Subsequent	19	11	63	68	37	0
Glottic						
Elective	14	0	21	29	7	7
Immediate	13	15	54	61	15	8
Subsequent	32	6	38	75	28	0

Table 13.47 - Cancer of the Larynx
Involvement of Nodes according to N-stage and level
Ipsilateral Node only (N=93)
Data of Moe et al.

		N-Stage			
Level	N	N0	N1	N2	N3
I	6	1	1	1	3
II	24	5	11	7	1
III	24	5	6	7	6
IV	12	3	1	2	6
V	7	0	1	2	4
Total	73	14	20	19	20

As one would expect, level II and III are the most frequently involved, contiguous with the level of the larynx in the neck. In a study of 159 patients with advanced laryngeal cancers submitted to conventional surgery, Moe et al. made the correlation between clinical N-stage and the involvement of the different levels. A clear hierarchical distribution of histologically positive nodes by level was found, as involvement of lower jugular, supraclavicular or submandibular nodes occurs only in more advanced neck disease (table 13.47).
According to Olsen et al., the Delphian node should be invaded in about 1% of the larynx cancer patients.

Non-Regional Lymph Node Metastases

As we will see later, mediastinal and even abdominal nodes have been reported in clinical and autopsy series, either in laryngeal cancer patients or in other head and neck cancers.
More rarely reported and usually neglected, both clinically and/or at autopsy, are the axillary nodes. Nelson et al. have reported on a patient where bilateral axillary dissection for positive nodes was done simultaneously with surgery for an advanced laryngeal cancer. The patient lived for 25 years after the treatment.

A number of other small series of patients with axillary nodes have been published, but the reports were not available.

Distant Metastases

While the incidence of distant metastases is very low for cancer of the larynx, the actual incidence will depends further on the number of glottic cancers included.

Kaiser et al. observed 2.7% distant metastases in 373 patients treated for a T1N0 glottic cancer, either by surgery or irradiation. Comparing radiotherapy with surgery for supraglottic cancer in a series of 302 patients, Suarez observed a correlation with the N-status, stage and treatment method. However, the group treated with RT had 3 to 4 times more Stage III-IV patients. Overall, the rate amounted to 12.6%.
In a series of 315 patients treated for aryepiglottic fold (margin) cancer, Spector et al. observed distant metastases in 15%.

For supraglottic cancers, DeSanto et al. mention an incidence of 13.2% after unilateral and 11.2% after bilateral neck dissection in a series of 222 patients. In 76 patients treated for marginal cancers with a minimum follow-up of 5 years, Lacourreye et al. observed distant metastases in 16%. Glanz et al. differentiated the observed number of metastases according to site. They observed 6/460 or 1% distant metastases in glottic cancer and 8/124 or 6.4% in supraglottic cancers.
As far back as 1961, Mumma et al. reported on 8 patients in a group of 430 consecutive patients treated for endolarynx cancer. Lung metastases were present in all. There were 6 with liver metastases and 3 with heart metastases. Two patients had metastases in bone, adrenal, kidney and bowel, one had a brain and one a skin metastasis.

Table 13. 48 - Cancer of the Larynx
Distant Metastases (N=26)
Data of Abramson et al. 1971

Lungs	21	Bone	9
Mediastin.nodes	15	Liver	7
Pleura	6	Abdominal nodes	5
Heart	2	Kidney	3
Brain	1	Adrenal	2
		Small intestine	1
		Spleen	1

The most adequate data, but only on 26 patients, of the metastatic pattern from cancer of the larynx were reported by Abramson et al. Reviewing the literature up to 1970, they noted an incidence of 38%.
The observed distant metastases are shown in table 13.48. It concerned 8 glottic and 18 supraglottic cancers. We are not aware of more recent data on the site distribution of distant metastases.
In 1967, Alonso et al. reported on 107 patients who developed distant metastases or 7.5% of 1,410 patients treated. Their data are almost completely based on clinical and surgical observations and include most probably a number of second primaries, as they mention 10 metastases in the oral cavity and 10 esophageal localisations. We brought these 87 patients in table 13.49.

Table 13. 49 - Cancer of the Larynx
Distant Metastases (N=87)
Data of Alonso (see text) 1967

Lungs	30	Kidney	2
Mediastinum	5	Urinary Bladder	3
Brain	6	Penis	1
Stomach	3	Bone	16
Duodenum	1	Colon	1
Abdomen	2		

Table 13. 50 - Cancer of the Larynx
Distant Bone Metastases

Site	Alonso	Abramson
Skull	3	1
Spine	3	3
Sternum	4	1
Ribs	--	1
Shoulder	1	--
Pelvis	--	2
Sacrum	1	--
Thigh (femur?)	1	--

Bone metastases are not uncommon in laryngeal cancer, but attention to them in the literature is very limited. With the exception of the previously mentioned series of Alonso and of Abramson, Loughran reported on 4 cases. They had metastases in the rib, the vertebrae, the fibula and the femur (table 13.50).

Pulmonary metastases have been reported in several patients. Differentiation with a second primary, a common occurrence in H&N cancers is necessary. Rendina et al. have reported on a series of 11 patients, referred for pulmonary metastasectomy. At thoracotomy, three patients were found to have a second primary. Histological differentiation is possible only when the bronchial primary has another histology, but radiology of the thorax can also determine the difference, with multiple miliary lesions and site within the lung indicative of metastasis.
We were somewhat surprised to find a relatively large number of case reports on patients with distant metastases in laryngeal cancer, compared with the other H&N sites (table 13.51).

It will be noticed that there are 8/27 or 30% cardiac metastases, also quoted in the above-mentioned series. Cutaneous metastases are a particular class. Stomal recurrences, the recurrences within the surgical scar and the cutaneous lymphangitis over nodes infiltrating the skin or from a recur-rence must be excluded. Nevertheless, several clear cases have been reported with skin metastases over the skull, the face, the chest and elsewhere (table 13.52).

Table 13. 51 -Cancer of the Larynx
Cases of Distant Metastases reported

Author	Pat	Primary	Site of M	Interv
Palmer 1964	M59	LaryngoPhar	Heart, gallblad	1mo
Palmer 1964	M49	Sin.Piriform	Heart, other	Aut.
Palmer 1964	M63	Supraglottic	Pericard, other	Aut
Palmer 1964	M58	Sin.Piriform	Heart,other	Aut
Basex 1967	M57	Supraglottic	Bo.ringfinger	17 mo
Silber 1969	M56	Supraglottic	Ri.kidney	3 mo
Harrer 1970	M63	Larynx	Heart	1 yr
Harrer 1970	M69	Larynx	Heart	??
Harrer 1970	M54	Larynx	Heart	??
Harrer 1970	M32	Larynx	Heart	??
Whalen 1988	M55	Larynx T3	Stomach	10 mo
Cohen 1972	M58	Larynx	Left hand(')	6 mo
Barton 1979	M58	Supraglottic	Heart LA	17 mo
Jordaens '83	M57	Glottis	Heart LV	10 yrs
Mitnick '85	M53	'larynx'	Kidney	5 mo
Zahra 1986	M67	Supraglottic	SinusCavern	1 mo
Mess 1986	M55	Larynx	Ri.index finger	??
Warwick '87	F62	Supraglottic	Ri.Temporal	5 mo
Francois '89	M59	Larynx	Small bowel	2 yrs
Shvili 1990	M72	Epiglottis	Nasal tip	4 yrs
Hamdam '91	M68	Larynx	Lung jejunum	3 yrs
Petot 1991	M78	Arytenoid	Duod.jejunum	1 yr
Huncharek'91	M70	Subglottis	Pleura plaque	8 mo
Perez 1992	M64	Epiglottis	Penis	1 yr
Airoldi 1993	M54	Supraglottic	Small bowel	7 yrs
Weiss 1994	F64	Supraglottic	Pituitary	9 mo
Yoshihara'97	M71	Supraglottic	Small bowel	2 yrs
Keiner 1997	M62	Supraglottis	Sphenoid sin.	6 mo
Paul 1999	M42	Supraglottic	Le.kidney	2 yrs
Choi 2000	M65	Larynx NOS	Le.Patella	1 yr

(') also widespread skin and liver, at autopsy many abdominal

Table 13. 52 - Cancer of the Larynx
Skin metastases reported

Author	Pat	Primary	Site of M	Interv
Veraldi 1988	M56	SupraglottisLe.arm-forehead		1 mo
Horiuchi 1992	M64	Larynx	Abdomen	2 mo
Debois 1996	M49	SupraGlottic	Presternal	3 mo
Bhandakar '97	M50	Larynx	Shoulder, toe, Scalp,	2 yrs

Causes of Death

Cancer of the larynx will kill more by locoregional spread and invasion, destroying important structures and impairing the nutrition and respiration of the patient. Local recurrences are thus more important than distant metastases as causes of death. Second primaries elsewhere also participate in the infaust evolution. In the series reported by Siirala et al.,

locoregional evolution was responsible for half of the deaths, distant metastases principally pulmonary, for 28%. Overall, the cancer was responsible for 80%, while other causes as suicide, cerebrovascular and other problems caused the death in the other patients.

METASTASES from Other H&N CANCERS

Most articles only give the number or a percentage of patients developing distant metastases without any information on site. Every oncologist knows that such patients can develop distant metastases, but would be surprised by the scanty attention the site distribution of distant metastases has received in the literature. Furthermore, the length of follow-up and the method of diagnosis is not always stated.

A group of Shangai (Sun et al.) has addressed the pulmonary metastases from H&N cancers. Unfortunately, they combined epitheliomas with sarcomas, as well as aberrant salivary gland histology. Valid conclusions can then not be made. The radiologic aspect of these metastases is, howver, not particularly different from other cancers, and solitary, multiple nodular, miliary, indistinct or irregularly shaped 'shadows' are observed. A better correlation with histology should have been done.

In spite of numerous articles addressing the cancer of the tongue either the mobile part or the base, we found mention of distant metastatic sites only in an old report of Robinson et al., dating back to 1965. Six of the 64 patients treated developed distant metastases, one in the lung, 1 in the base of the skull, 2 in the supraclavicular region and 2 in the axilla.

Of a group of 471 patients with tonsillar carcinoma, 72 or 15% developed distant metastases (Chung et al.). Autopsy detected metastases in 27, confirming it in 6. Single organ metastases occurred in 42 or 58% (table 13.53). The relatively high number of abdominal metastases should be noted.

Table 13. 53 - Cancer of the Tonsilla (incl.pillar)
Distant Metastases confirmed (N= 72/471)
Data of Chung et al. (1980)

Supra-Diaphragmatic		Infra-Diaphragmatic	
Brain	7%	Liver	29%
Thyroid	6	Small bowel	8
Lung	58	Mesentery	6
Heart	6	Spleen	8
Mediastinum	14	Adrenal	7
Pleura	7	Kidney	11
Distant nodes	17	Other GIT	9
Bone	22		

Of the 126 consecutive patients treated for a cancer of the floor of the mouth, Nakissa et al. reported that 20, or 17% developed distant metastases. The data are in table 13.54, and show the high number of lung metastases as one would expect.

As far as sinusal carcinoma is concerned, we found a report of Kent et al. (1984) on 250 patients, of whom 20, or less than 10%, developed distant metastases (table 13.55). It will be seen that 6 had brain metastases, to be differentiated from contiguous invasion.

Table 13. 54 - Cancer of the Floor of the Mouth
Distant metastases 20 of 126 patients
Data of Nakissa et al. 1978

Lung	14 cases
Pleura	2
Spine and Clavicle	5
Liver	3
Diaphragm	1
Mediastinal nodes	1
Parotid gland	1

Table 13. 55 -
Cancer of the Nasal Cavity -Paranasal Sinuses
Distant Metastases (N=20/250)
Data of Kent et al. 1984

Lung	9cases	Bone	
Brain	6	Cervical spine	2 cases
Liver	6	Thor-Lumb. vert.	8
Kidney	3	Skull	6
		Ribs	3
		Femur	2

Table 13.56 - Cancer of the Hypopharynx
Distant Metastases in 80 of 215 patients
Data of Stefani et al. 1971

Site	N	Site	N
Brain	7 cases	Liver	22 (28%)
Mediast.Nodes	30	Kidney	7
Lung	48 (60%)	Adrenal	7
Heart	5	Other sites	14
Other thorax	13	Bone	12

Of 215 patients treated for a cancer of the hypopharynx, 80 or 37% patients developed distant metastases, a figure regularly quoted for this cancer site (Stefani et al. 1971). They are the only authors who have reported data on the sites of the metastases (table 13.56).

Driscoll et al. reviewed 75 patients with cancer of the pyriform sinus with a follow-up time of 5 years. Distant metastases developed in 17, or 23%. Six patients had multiple metastases. There were 13 lung metastases, 3 in the liver, 2 in the brain, 6 in the bone and 1 in the GIT. Several case-reports on metastases from H&N cancers have been published (table 13.57).

Other Metastases

Metastases to the skin have been reported in some small series. They need to be distinguished from recurrences in the surgical scar and possibly local infiltrating lymphangitic metastases over the neck. Of the 12 patients reported by Kmucha et al., some had metastases on the back and the chest, while some had them in the neck. Only three patients had single

Table 13. 57 - Cancer of the Head Neck
Case reports on distant metastases (')

Floor of the Mouth			Interval
Komminoth 1977	M52	Finger IV	1 year
Buccal Mucosa			
Mathew 1997	M35	Thorac.Vertebra 12	2 yrs
Tonsil			
Katzner 1984	M59	Subtrochanteric #	30 mo
Katzner 1984	F61	Ri Femur neck	2 yrs
Smith 1986	M45	Heart RV	??
Lesur 1988	M90	Ileum	3 yrs
Day 1995	M56	Orbit	1 wk
Tongue			
Zatuchni 1981	M61	Heart RV	2 yrs
Zatuchni 1981	M62	Heart myocardium	2 yrs
Rozboril 1983	M55	Sternoclavic.joint	simult.
Katzner 1984	M??	Femur subtrochanteric	6 mo
Katzner 1984	M45	Femur trochanter	??
Werbel 1985	F61	Heart right atrium	18 mo
Roblot 1987	M73	Femur Gr.Trochanter	Reveal
Stone 1988	M74	Pelvic mass	6 mo
Rivkin 1999	M57	Right ventricle	3 mo
Soft Palate			
Creaven 1972	M39	Skin nodules, Axillary Lung, abdomen	simult.
Gingiva			
Viswanathan '96	M70	Ri.Middle finger	2 yrs
Ishikawa 1999	M74	Pleura	2 mo
Yamamoto 2000	M68	Pulm.Lymphang.	30 mo
Ethmoid Sinus			
Vizel 1981	F23	Breast	6 mo
Johns 1987	M47	L1 spin.cord compres	7 mo
Murphy 1991	M59	Cerebellum vermis	18 mo
Murphy 1991	M57	Cerebellum	2 yrs
Nguyen 1992	M70	Head of Pancreas	15 yrs
DeVos 1999	M55	Meningeal Carcin.	Simult
Sinus Piriformis			
Roux 1981	M52	Sphenoidal Sinus	2mo
Katzner 1984	M65	Humerus #	6 mo
Glick 1985	M49	Gastric cardia	7mo
Petit et al. 1995	M45	Rectosigmoid	18mo
Ginies 1999	M44	Pancreas head	Reveal.
Hypopharynx			
Zieske 1988	M67	Pulm. Lymphangitis	1 month
Nakamura '96	M43	Temporal bone	2 mo
	M59	Temporal bone	1 month
Wu 1996	M68	Stomach duodenum	2yrs
Hsu 1998	M49	Peritoneum	3 mo
Hsu 1998	M55	Vertebra T3 - Periton	6 mo
Mussari 1999	M70	Choroid Le.Eye	1 year

(') excluding nasopharynx and larynx proper

evident metastases. Another small series was reported by Pitman et al. While four had metastases at the face, 2 at the chest, 1 at the abdomen, 9 had them in the neck and 3 other patients had multiple sites involved. A case was reported by Schultz et al. of a hypopharynx cancer metastatic to the skin at the flank.

Several acral lesions mimicking vasculitis though histologically confirmed as metastatic epidermoid carcinoma were the revealing sign of a hypopharyngeal carcinoma in a M43 (Nigro et al.).

A somewhat more detailed study of pulmonary metastases has been reported by Piquet et al. They noted that the hypopharyngeal cancers had the highest frequency, (57%), while glottic tumors had only 3.5%. Supraglottic cancers had an incidence of 36%. The radiological appearance varies from solitary infiltrates or nodules to the multiple 'cannon-ball' aspect.

A number of case reports for different primary sites have appeared in the literature. There is apparently no specific pattern. We give them here in table 13.57 for documentary purposes. We do not claim completeness, as a number of reports cited in the reference lists were not available.
The pleural metastasis quoted by Ishikawa et al. seemson the basis of the CT showed to be an anterior supradiaphragmatic node.
As far as metastases to the breast are concerned, a number of cases have been mentioned in the series of patients with metastases to the breast. They are summarized in table 13.58.

Table 13.58 -Head and Neck Cancer
Primaries with Metastases to the Breast
as reported in series

Hajdu 1972	Maxillary sinus
Toombs 1977	Tongue
Tooms 1977	Floor of the mouth
Solow 1979	Tongue

METASTASES from THYROID CANCER

Four main histologic types are distinguished:

1. Papillary Cancer,
2. Follicular Cancer,
3. Anaplastic Carcinoma and
4. Medullary Cancer.

The two first are grouped together as differentiated cancers. A number of histological variants as oxyphil, tall-cell and Hürthle cell have been described. They present in the lower age groups, while anaplastic concerns more the older age groups. Medullary cancer, tumor of the C-calcitonin cells, is discussed subsequently.

Thyroid cancer has a relatively high rate of local and lymphatic invasion, with a low rate of distant metastases. There is some difference according to the histologic type concerned.

As far as metastases are concerned, thyroid cancers demonstrate some distinctive features:

1. The slow evolution, except for the anaplastic cancers, needs long follow-up or observation time.
2. This results in the possibility of metastases occurring very late after first treatment.
3. A minority of the distant metastases will be type 1 or revealing.
4. Occult cancer of the thyroid is not uncommon, to the extent that metastatic lymph nodes are found without a clinically detectable thyroid tumor. Usually only microscopic foci are found at thyroidectomy.
4. Due to their particular physiology, some metastases are revealed by the hyperfunction syndrome because of a high amount of thyroid hormone produced.
5. Some patients are reported to have had a long standing-goiter, which apparently become malignant. It can be inferred that the goiter was probably malignant all along, but with a slow evolution, and its malignancy revealed only by the metastases.

Loco-Regional Spread

The thyroid malignancy will first expand within the thyroid gland locally and possibly intrathyroidally towards the other lobe. When it invades its capsule, the way is open to invade neighbouring tissues and structures as the larynx, the esophagus and the vascular trunk. Lymphatic spread occcurs early in development as the thyroid gland has a rich lymphatic network.

Problems in Loco-Regional Invasion

Loco-regional complications are highly dreaded. The invasion of thyroid cancer into the laryngeal and pharyngeal structure will ultimately cause obstruction of the airway and fatal hemorrhages. The symptomatology of different series is grouped on table 13.59.

Table 13.59 - Cancer of the Thyroid Gland
Symptoms of Aerodigestive Invasion

	Calcaterra N=44 (1981)	Tsumori N=18(1985)	Lipton N=48(1987)
Dyspnea	34%	65%(')	--
Dysphagia	30	--	4%
Hoarseness	23	72%	23
Throat pain	9	--	(1)
Hemoptysis	4	38%	6%
Stridor	--	--	35%

(') more than grade II.

As always, different series have different symptom rates, either due to different appreciation or due to selection of cases. In any case, dyspnea is most important along with hoarseness, both expressing the narrowing of the laryngeal air space. In the series of Tsumori, the majority (13/18) were of the papillary type. One squamous cancer was included, probably not a thyroid primary. Of the 44 cases of Calcaterra, there were 6 anaplastic, the most malignant type.

Routes of Invasion

Invasion mainly yakes place because of the close proximity of tumor to the cartilage. The most frequently invaded sites are the trachea, the recurrent nerves, the esophagus and the larynx. The tumor follows the overlying muscular planes.
In one case (M76), the progressive contiguous growth of a biopsy confirmed well differentiated papillary thyroid carcinoma towards the cervical spine with destruction of the corpus of the vertebrae resulting in quadriparesis (Ginsberg et al.).
MacCaffrey et al. have also provided data concerning the sites of invasion in 262 patients with invasive papillary cancers (table 13.60). The high incidence of the involvement of the strap muscles and of the M.Sterno-Cleidomastoideus (MSCM) is to be noted.

Table 13.60 - Invasive Papillary Thyroid Cancer
Involvement of Neighbouring Structures (N=262)
Data of MacCaffrey et al. 1994

Muscle Only	56 or	21.3%
Anter. Strap of M. SCM	138	52.6
Trachea	96	36.6
Laryngeal Nerve	123	49.6
Esophagus	56	21.3
Larynx	30	11.4
Other(')	77	29.3

(') jugular vein, carotid artery, prevertebral fascia

Invasion of the larynx occurs by direct extension, as the ossified cartilage will not resist invasion. The tumor will proceed through the cartilage, either thyroid or cricoid, or in the paraglottic space after it has turned around the cartilage (fig. 13.17).

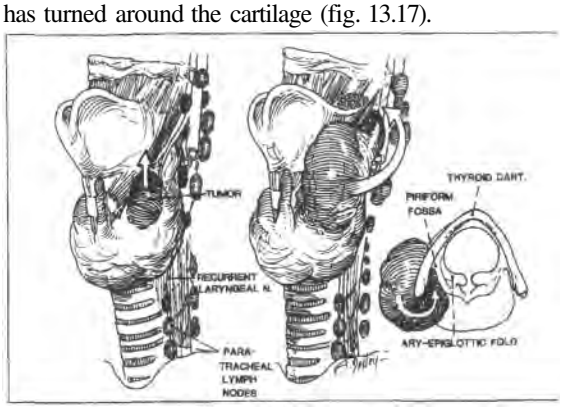

Fig.13.17 - (left) direct invasion of the thyroid cartilage; (right) invasion of the paraglottic space wrapping around the posterior edge of the thyroid cartilage (from MacCaffrey et al., with permission)

The pharynx is usually invaded by a posterior extension of the tumor around the thyroid cartilage and into the sinus piriformis (fig. 13.18. When its wall is invaded, intraluminal extension is frequent and will cause dysphagia with the risk of hemorrhage.
The esophagus is usually invaded by direct extension or invasion from a metastatic lymph node (fig. 13.19).

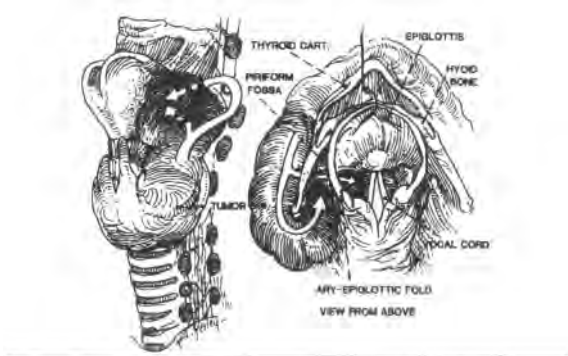

Fig.13.18 - Invasion of the sinus piriformis and pharynx by extension around or through the thyroid cartilage (from MacCaffrey et al., with permission)

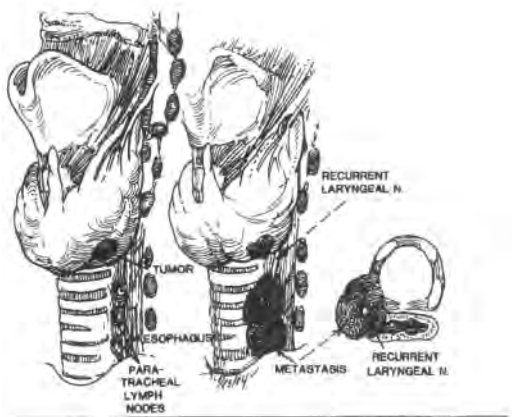

Fig.13.19 - Invasion of the recurrent nerve, tracheal wall and esophagus by extension from a metastatic paratracheal lymph node (from MacCaffrey et al., with permission)

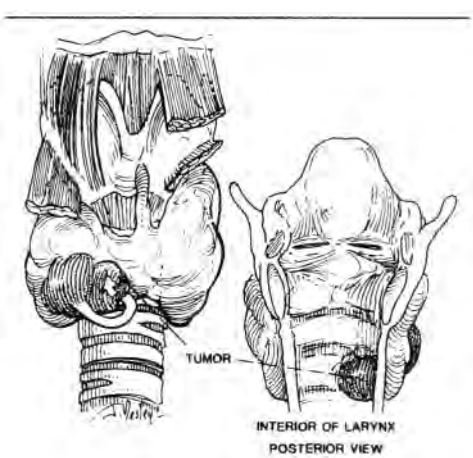

Fig.13.20 - Invasion of the trachea anteriorly through the cartilage or between the tracheal rings (from MacCaffrey et al., with permission)

Tracheal invasion occurs through direct inferior extension or from invasion of a paratracheal metastatic lymph node (fig. 13.20) (MacCaffrey et al.). Shin et al. have described four stages of the airway invasion.

Lymphatic Spread

For thyroid carcinoma, the regional nodes are the cervical and those in the upper mediastinum. The cervical nodes of the thyroid are situated between the middle and posterior neck fascia. The anterior and posterior chain is separated by the carotid. As there is no anatomical structure, the virtual boundary to the mediastinal nodes is the vena brachiocephalica sinistra and the truncus arteriosus brachiocephalicus dexter. The lower boundary is at the height of the carina. (fig.13.21).

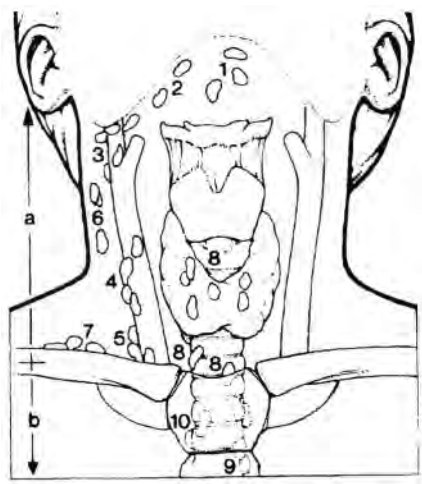

Fig.13.21 - The various lymph chains and stations tributary to thyroid cancer

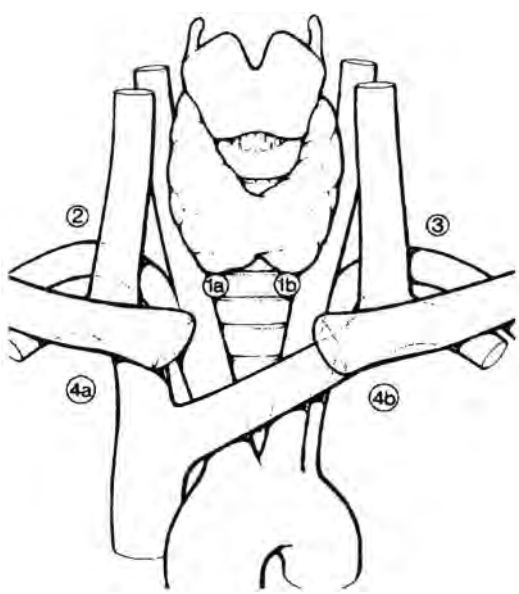

Fig.13.22 - The various compartment in which for lymph node metastases may develop (from Dralle et al., with permission)
Compartiment 1. Central between the carotids, a: right, b. left; 2. Cervico lateral right; 3. Cervico lateral left; 4.a. right mediastinal; 4. b. left mediastinal

However, as the metastatic lymph nodes have a certain volume and disrupt the anatomy of the neck, a more appropriate classification has been proposed, dividing the neck into a number of compartments (fig.13.22).

The lymph nodes have been categorized as follows

1. Submental nodes
2. Submandibular
3. Jugular-cranial
4. Medial jugular
5. Inferior jugular
6. Cervicodorsal (')
7. Supraclavicular
8. Prelaryngeal
9. Mediastinal-anterior
10. Mediastinal-posterior

As a reminder, below is the official TNM code in repect of the thyroid lymph nodes:

pNO: at least six nodes examined and negative
pN1a: homolateral cervical nodes invaded,
pN1b: positive lymph node in the middle neck, heterolateral or in the mediastinum.

The frequency of the invaded lymph nodes in lymph-adenectomies has been reported by Dralle et al. (table 13.61). The progressive increase in the frequency of invasion of each compartment permits the conclusion that the invasion occurs in an orderly way.

Table 13.61 - Cancer of the Thyroid Gland
Frequency of Invasion of the Compartments
Data of Dralle et al.

Compartment		
1.	Ipsilat. Cervicocentral	42-86%
2.	Ipsilat. Cervicolateral	32-68%
3.	Contralateral Cervicolateral	12-24%
4.	Mediastinal	3-20%

As we have already noted for several cancers, adequate data on the involvement of lymph nodes in the different locations are almost non-existant. Only a few reports provide some adequate data, though according to the different lymph node groups. In a series of 117 patients younger than 20 years, about half of them had positive nodes at surgery (Frankenthaler et al.) (table 13.62).

Table 13.62 - Differentiated Thyroid Cancer
Lymph Node Metastases (N=117)
Data of Frankenthaler et al. 1990

Upper Jugular	30%
Mid Jugular	45%
Lower Jugular	52%
Lower Spinal Access.	33%
Upper and Mid-Spinal	0%

More detailed data were discussed by Rossi (fig. 13.23), confirming the high incidence of nodes along the jugular chain.

There is an abundant literature on thyroid carcinomas presenting first as a cervical node with a clinically occult thyroid carcinoma. We will not discuss that problem.Involvement of non-regional lymph nodes such as the axillary ones is mentioned in some case reports.

The presentation of thyroid cancers, particularly that of the papillary type, with cervical node(s) first, and an occult thyroid tumor is well known. Nevertheless, presentations with nodes in the neck, as distinct from the cervical will also occur.

Some reports describe nodes low in the neck, others behind the sternocleidomastoideus muscle or retro-pharyngeal. Description is not always clear so they are difficult to review. Para-pharyngeal nodal extension high in the fossa infratemporalis at the jugular fossa has also been reported as first presen-tation of papillary carcinoma (Sirotnak et al.).

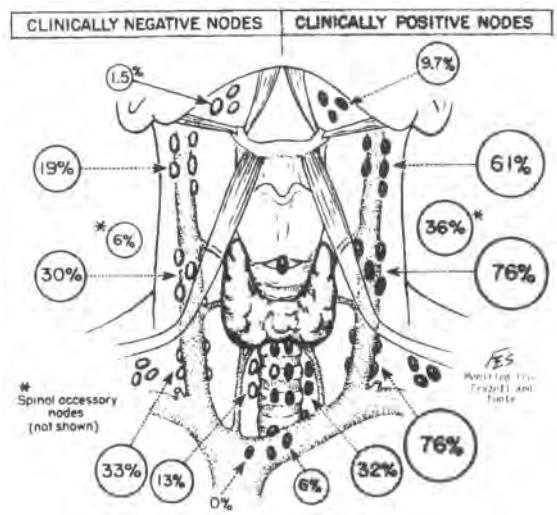

Fig.13.23 - Distribution of Lymph Node metastases (Review of Rossi, with permission)

Distant Metastases

As for many other cancers, large autopsy data are virtually absent, more because of the low rate and probably because the slow growth of cancer and its inherent low death rate, except perhaps for anaplastic carcinoma. Nevertheless, for the latter almost no data have been published. A report dating from 1964 concerning 193 autopsies gives adequate data according to histology (Silliphant et al.) (table 13.63). Of these patients 107 had metastases, while the other died from other causes.

Some data must be regarded with caution in view of the small numbers of some histologies, but the trend is quite comparable with the series discussed below.

The few reported series, with a comparatively restricted follow-up time, show a distant metastatic rate of 5 to 8%. One of the oldest report is from Rasmusson in 1978, with data according to histology (table 13.64).

From these limited data one can tentatively conclude that anaplastic cancers have a somewhat higher rate, and papillary the lowest.

Table 13.63 - Cancer of the Thyroid
Regional and Distant Metastases at Autopsy (N=193)
Data of Silliphant et al 1964

	Pap	Foll	Mixed	Ana	Total
N=	18	18	8	63	107
Nodes	89	78	100	76	86
Homolat	83	61	87	59	75
Contralat	28	11	23	16	20
Mediast.	56	33	25	36	41
Other	17	--	12	27	9
Lung	56	44	50	84	50
Bone	17	44	75	40	39
Liver	17	22	50	38	25
Adrenal	6	17	50	25	18
Brain	17	17	38	22	20
Heart	22	6	50	21	20
Kidney	11	11	25	22	14

Table 13.64 - Carcinoma of the Thyroid
Distant Metastases according to Histology (N=227)
Data of Rasmusson

	Papill			Follic.			Anaplast.			Total		
Site	a	b	c	a	b	c	a	b	c	a	b	c (')
Nodes	72	13	(4)	16	4	(1)	24	4	(5)	150	66	(20%)
Lungs	12	8	(6)	1	2	(2)	9	2	(8)	38	17	(36%)
Bones	3	4	(1)	12	1	(1)	0	2	(4)	27	12	(12%)
Liver	0	1	(1)	0	1	(0)	0	2	(5)	5	2	(16%)
Brain	0	1	(0)	0	1	(0)	0	1	(0)	3	1	(-)
Skin	0	2	(0)	0	1	(0)	0	0	(0)	3	1	(-)

(') at diagnosis (b) in follow-up;
(c) at autopsy for 50 patients.

Two other small series have reported limited data. Of 435 patients, Schindel et al. observed pulmonary metasta-ses in 2.5%, bone metastases in 1.4% and local tracheo-esophageal involvement in 3.7%. In 514 patients with differentiated thyroid cancers, Mizukami et al. observed 34 or (6.6%) distant metastases, 5 only at autopsy. Pulmonary metastases were also the most frequent; 82% of all metastases. Bone metastases where the second most frequent, with 44%. The other sites were the pleura, brain, liver, kidneys, pericard and diaphragm, each with less than 20%.
Of 187 patients with a well-differentiated (papillary and follicular) tumors, 11 or 6% had metastases, of which 70% were pulmonary metastases.

Interesting data have been provided by Dinneen et al. In 1800 patients with papillary cancers, they observed 100 or 5.5% with metastases at presentation. Pulmonary metastases were present in 71 patients, 60 as sole presentation. Twenty had bone metastases, 15 only this site. Mediastinal nodes were present in 10%. Subsequent metastases were observed in 32 of these patients, the majority (one third) brain metastases, but also 9 bone and 8 new lung metastases. The third 'wave' consisted also mainly of brain metastases, 4 of ten. This can very well be explained by a cascade, where the lungs are the first organ reached, from where other metastases will be seeded.
A similar pattern has been described earlier by Dargent. Of 252 patients with metastases, 157 were seen at first diagnosis and 95 later. Pulmonary metastases accounted for 14%, but there were 22% bone metastases, probably due to a later overall stage of the patients.

According to histology, the risk of distant metastases was 2.3% for papillary, 10.5% for follicular and 12.2% for the rare Hürthle-type, in the series of 44 patients presenting initially with a distant metastasis (Shaha et al.). Pomorski et al. have reported on 26 such patients of a group of 975, or 2.6% presenting with nodal or distant metastases first. Mainly bone metastases were involved, half of those with distant metastases.

In 70 fatal cases with papillary cancers, Tollefsen et al. found 51% pulmonary metastases, 25% bone and 10% brain metastases. In 87%, there were locoregional metastatic lymph nodes. Also in respect of papillary cancers, Carcangiu et al. have reported interesting observations in 241 cases (table 13.65). This confirms that both differentiated cancers have about the same metastatic rate. Other influential factors were the absence of a tumor capsule and an infiltrative margin.

Table 13. 65 - Carcinoma of the Thyroid
Evolution of 241 patients -Data of Carcangiu et al.

Node metastases	54.3%			
Lung metastases	14.1%			
Other distant	5.4%			
Size/histology	<1.1cm	>1cm	Papill	Follic
Node Metast.	64.5%	47.3%	48.4%	47.4%
Distant	3.2	19.1		
Lung metastases	nd(')	nd	10.6%	21.0%
Other	nd	nd	4%	2.6%

nd : no data

Table 13.66 - Carcinoma of the Thyroid
Autopsy Data according to Histology
Data of Heitz et al.

Site of M	Follicular N=51	Papillary N=14	Anaplastic N=80
NONE	15	6	7
Nodes Cerv	14	7	43
Nodes Oth	17	2	47
Lungs	29	6	60
Pleura	11	3	40
Diaphragm	0	0	5
GIT	2	0	18
Liver	1	1	15
Kidneys	3	1	13
Adrenals	2	1	16
Spleen	0	0	1
Brain	4	1	6
Skin	1	1	6
Bones	35	5	37

Data at autopsy in 156 patientshave been reported according to histology by Heitz et al. In 66 patients no metastases were found (table 13.66). They include

the only data available for anaplastic cancers. The aggressiveness of the anaplastic cancers has been frequently demonstrated. In spite of the low number of papillary cancers, the proportion of metastases is high.

The most adequate dat have been reported by Hermann et al. on 892 patients, of whom 572 differentiated and including further 36 cases of lymphomas, bringing certain bias in the data. In 151 patients distant metastases were found, 83 concerned only one organ. The data were obtained by clinical, imaging and autopsy methods (table 13.67).

Table 13. 67 - Carcinoma of the Thyroid
Distant Metastases in 151 / 892 patients
Data of Hermann et al. (1987)

Supra-Diaphragmatic			
Lungs	71%	Bone	37%
Pleura	21%	Brain	2%
Heart	11%	Spinal Cord	0.7%
Infra-Diaphragmatic			
Kidney	15%	Peritoneum	2.6%
Liver	13	Stomach-Intestine	2.0%
Adrenals	9	Spleen	1..3%
Pancreas	3%	Gallbladder	0.7%
Ovaries	(0.7%)		

These authors have also examined the influence of stage at diagnosis and of histology. As expected, stage is strongly influencial (table 13.68), while histology seems to have a somewhat varied influence (table 13.69). The number of pulmonary and bone metastases is undoubtedly proportionally higher in the follicular group. The 269 cases of papillary and 303 cases of follicular cancer permit a reasonable estimate of the incidence of metastases but higher in the anaplastic group, 40/139 or 28%.

Table 13.68 - Carcinoma of the Thyroid
Distant metastases according to Stage of Disease
Data of Hermann et al. N=151

	N	I	II	III	IV
Histology					
Papillary	11	2	0	3	6
Follicular	43	2	5	9	27
Medullary	6	0	0	2	4
Anaplastic	40	0	0	3	37
Sarcoma	41	0	0	2	39
Lymphoma	10	0	0	0	10

Table 13.69 - Carcinoma of the Thyroid
Distant metastases according to Histology (N=151)
Data of Hermann et al.

Site	Pap	Fol	Med	Ana
Only 1 organ	8	29	2	20
Lung	6	24	3	32
Bone	6	29	5	11
Pleura	2	5	1	7
Kidney	0	4	1	6
Adrenal	0	4	0	5
Heart	0	2	0	6

Reviewing 327 patients below 21 years of age, LaQuaglia et al. looked for the risk factors predisposing the patient to distant metastases in the 83 patients who developed metastases. The only significant factors were extra-thyroidal extension observed at first surgery, the presence of positive regional nodes and a limited nodule excision as first treatment. Tumor size, histology type and types of symptomatology were not found to be significant.

Pulmonary Metastases

Being the first organ reached by cells from a thyroid tumor, the lung will be quite frequently involved. The literature is relatively silent on this topic. Woolner et al. quote the figure of 3.8% of lung metastases in papillary carcinoma during the whole observation period. In 845 patients, Nemec et al. were able to find 123 with any pulmonary metastases or 14.5%.
These authors were also the first to systematize the radiological aspects of the lung metastases. Chest X-ray remains a sensitive method, although CT will detect more metastases. It should be remembered that in about 1 to 5%, only the radionuclide (I-131) scan will detect the active pulmonary metastases (table 13.70).

Table 13.70 - Carcinoma of the Thyroid Gland
Radiologic Features of Pulmonary Metastases (N=112)
Data of Nemec et al.1979

Micronodular (pseudomiliary or micronodular)	34%
Macronodular (multiple)	44%
Single Macronodular	18%
Nodes at Lung Hilus	2.5%
Pleural metastases	less than 2%

They could not find any particular propensity according to histology type, except somewhat more macronodular metastases in the follicular type. There were also other, mainly bone metastases in about half of the patients,.
Massin et al. followed a similar classification, but noticed that the macronodular group could be divided in patients with or without mediastinal nodes. As far as the timing of the diagnosis is concerned, 34 of the 58 patients had early or simultaneous pulmonary metastases, while in the 24 others, the interval varied from 1 to 24 years after surgery.
If the imaging features are taken in account, one can distinguish three groups (Casara et al.):

1. negative chest X-rays and positive scan,
2. positive chest X-rays and scan,
3. positive chest X-rays and negative scan.

The authors found proportionally more male patients with lung metastases than expected. There were relatively more papillary tumors in the first group, with more follicular in the other and the prevalence of cervical lymph nodes was high in the three groups. Remarkable is that in group 1, the patients only had lung

metastases, probably at an early stage.
Another series was reported by Dromer et al. They observed pulmonary metastases in 7.5% of their 750 thyroid cancer patients. A macronodular aspect was seen in 80% of the 56 patients. A more important aspect is the fact that in half of the patients with pulmonary metastases, they were the revealing sign of a thyroid cancer or found simultaneously with the primary. When found in the follow-up, the longest interval was 15 years.

Lung metastases not visible on chest X-rays and detected with radioiodine amounted to 23 patients of a series of 1,500 patients, or 1.5% (Schlumberger et al.). In the series of Samaan et al. with 1,127 patients, there were 10 patients or 0.8%. They had 49 positive at X-rays and with radioiodine.

In children, the frequency clearly depends on age, the lower age group having a higher frequency. This was documented by Vassilopoulou et al. The frequency decreases from 15% in the 4-12 age group to 3.5% in the 20-25 age group. Children almost always have only micronodular metastases. Similar data reported by Carcangiu et al., show that 50% of patients aged between 11 and 20 years had pulmonary metastases.
Pulmonary metastases were seen at autopsy in 36 or 51% of the patients who have died of thyroid cancer (Tollefsen et al.). Only 5 also had pleural metastases and/or effusion.

The main symptoms, when present, are cough and dyspnea. Hemoptysis is very rare. According to Woolner et al., only 6 of the 885 patients presented with hemoptysis, all 6 having an unknwon cancer. One case (M23) was reported by Blass et al.
A solitary lesion in the right middle lobe was reported in a F75, 47 years after surgery (Fonseca).
Two patients were reported by Strate et al. where the thyroid papillary cancer was detected only after a chest X-ray for symptomatic pulmonary metastases and confirmed at surgery to be papillary carcinoma.

Mediastinal Involvement

Two kinds of mediastinal involvement by a thyroid carcinoma may occur, extension of the tumor itself and metastatic lymph nodes in the mediastinum.
According to Torre et al., extension towards the mediastinum of the tumorous thyroid gland is observed in about 10% of the patients. They noted 30 patients in a consecutive series of 330 patients. Apart from the cervical mass observed in 93% and a cervical adenopathy in 66%, dyspnea was noted in 70%, dysphagia in 30% and dysphonia in 7%. Hyperfunction was seen in 2 patients. Of the 30 patients, there were 21 differentiated tumors, 4 anaplastic and even 5 medullary cancers.

Mediastinal lymph nodes involvement probably occur by further lymphatic spread from the cervical chains (fig. 13.24). Sarrazin et al. have addressed this aspect specifically. They noted an incidence of 2% for differentiated cancers and of 7.6% for all types, probably due to a high incidence of anaplastic cancers. The nodes were found in several nodal groups, but not all groups were involved. The nodes appeared between 3 months and 10 years after first surgery.

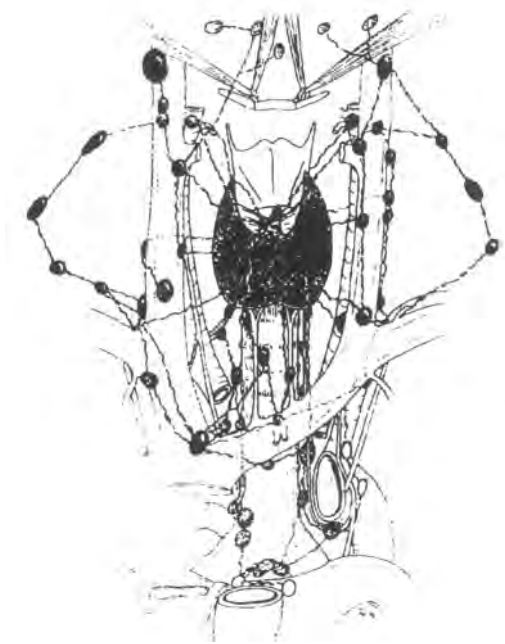

Fig.13.24 - The anatomical relationship between the cervical and mediastinal nodes involved by thyroid carcinoma metastases (Sarrazin et al.)

Twenty-one patients underwent a mediastinal lymph node dissection when nodes were suggested on CT or scintigrams (4 patients) or when a large tumor extended to the upper mediastinum (17 patients) (Sugenoya et al.). There were more positive cervical contralateral lymph nodes in the patients with mediastinal nodes.
Although the patient number were relatively low, the authors conclude that there are 3 pathways towards the mediastinal nodes in thyroid cancer:

1. spread from theadjacent cervical nodes (pre- and para-tracheal), along the recurrent laryngeal nerves towards the area of the vena brachiocephalica;
2. when bilateral cervical involvement is present, a risk of overflow to the mediastinal nodes is important;
3. the presence of pulmonary metastases can also result in mediastinal nodes.

An unusual case was reported by Higashiyama et al. A micrometastasis of follicular carcinoma was seen in a metastatic node from a squamous cell cancer of the bronchus, but the thyroid was found to be normal., The thyroid tumor was found four years later.

Brain Metastases

In 70 fatal cases of papillary carcinoma, Tollefsen et al. found seven patients with brain metastases, two of them also having orbital metastases.

Metastases to the brain in thyroid cancer are rare. Of 3,117 patients with thyroid carcinoma treated over a period of 51 years, 47 or 1.5% had cerebral metastases at any time of the evolution. In 36, it was diagnosed before death and in three it was the only metastatic site. Unfortunately, the authors did not report data on site location (Chiu et al.). Venkatesh et al. reported on 11 cases, also omitting to report sites. Salvati et al. reported on 6 cases, frontal in 3, temporal in 2 and parietal in 1. In a series of 241 papillary cancers, Carcangiu et al. found only 2 cases with cerebral metastases. Available literature data are in table 13.71.

Table 13.71 - Carcinoma of the Thyroid Gland
Cerebral Metastases Reported

Author	Pat	Histol	Site	Interval
Takeda 1970	F33	Papill	Ri.Frontal	Reveal(°)
Holmquest '76	M56	Papill	Ri.Parietal	2 mo
Carcangiu '85	F32	Papill	Ri.Parietal	no data
Carcangiu '85	F50	Papill	C.P.angle	no data
Parker 1986	M67	Papill	Ri.FrontoPar	2 yrs
Parker 1986	M79	Papill	Ri.Temp.Pariet	5 yrs
Michie 1987	M47	Papill	Le.Occipit	Reveal
Vilette 1990	M73	Follic	Ri.Parietal	Reveal
Goolden 1990	F52	Papill	Ri.Frontal	4 yrs
Biswal 1994	F26	Papill	Ri.Frontal	6 mo
Biswal 1994	M47	Follic	Le.Temporal	10 yrs
Biswal 1994	F54	Follic	Le Front+Temp	2 yrs
Biswal 1994	F46	Follic	Ri.Parietal	11 yrs
Biswal 1994	F04	Follic	Le.Front+Parasag	1 yr
Jyothirmayi '95	M51	Papill	Cerebellum	19 yrs
	M59	Papill	Ri.Frontal	18 mo
Pacak 1998	F82	Papill	Cerebellum	8 yrs
Abarca 1999	M38	Papill	Ri.Pariet+Ventr	4 yrs
Kapusta 1999	F43	Papill	Ri.Frontal	36yrs(')
Imamura 2000	M53	Papill(")	Front+Occip	Reveal
Maruyama 2000	M52	Papill	Le.Fronta	8 yrs

(°) seven months later the primary was found
(') diagnosis by FNAB; (") diffuse sclerosing variant.

This demonstrates not only the low frequency of cerebral metastases, but also the low report-rate.
Almost all cerebral metastases were single except in two patients where two metastases were seen. In only one patient, was it the revealing factor.
The predominance of papillary cancers is striking, as well as the two cerebellar metastases, these being rather rare. A patient (F40) with one cerebellar metastasis and multiple other hemorrhagic (cystic) metastases in the posterior fossa was reported. Excision revealed a metastatic papillary thyroid carcinoma, confirmed at CT of the neck (Isoda et al.). The same patient had also multiple cutaneous metastases at the anterior trunk.

The acumulation of large series in several institutes should allow more informative reviews. Fifteen patients from a series of 1,944 or 0.77% were reported by Samuel et al. There were 4 male patients, 9 had multiple brain metastases and one had a cerebellar location. Only one patient had a solitary metastasis, with no other metastatic site being involved.

Recently, Misaki et al. reported on 9 patients from a consecutive series of 167 (0.5%) treated thyroid cancer patients. All also had lung metastases and 4 had bone metastases. One had also a scalp metastasis. Seven of them were papillary and 2 follicular cancers. The metastases were multiple in 3 and there were three localisations within the cerebellum.
A M46 presented with progressive quadriparesis and pain in the neck. An enlarged thyroid was noted though a myelogram disclosed an intramedullary tumor. The latter was found to be a metastasis of a follicular thyroid cancer confirmed at thyroidectomy (Winkelman et al.).

Head and Neck Metastases

In addition to the invasion of larynx and pharynx as was discussed above, some patients have been reported where metastases occurred in this region. The majority are in the sinonasal cavity, frequently with involvement of the skull base, either at the lamina cribriformis or at the clivus. Some are complicated with neck nodes or even Horner's syndrome (table 13.72). Symptomatology is dominated by pain and/or hemoptysis.

Table 13.72 - Carcinoma of the Thyroid Gland
Head and Neck - SinoNasal Metastases Reported

Author	Pat	Histol	Site	Interval
Cinberg 1980	F80	Follic	Sin.Maxill	16 yrs
Chang 1983	F50	Mixed	Sin.Sphen	8 yrs
Renner 1984	F61	Follic	SinoNasal	3 yrs
Cumberworth'94	F62	Follic	SinoNasal	12 yrs
Yamasoba '94	F34	Follic	SinoNasal	Reveal
Freeman '96	M50	Papill.	Ethm.Nasal	3 mo
Altman '97	M81	Follic	Pansinusal	12 yrs
Hefer 1998	M58	Follic	Sin.Maxill	6 mo

Table 13. 73 - Carcinoma of the Thyroid Gland
Head and Neck - Oral Metastases Reported

Author	Pat	Histol	Site	Interval
Ripp 1977	F61	Carcin.	Ri.Mandible	12 yrs
Draper 1979	F65	Follic	Le.Mandible	16 mo
Nishimura '82	F74	Follic	Ri.Mandible	10yrs(')
Nishimura '82	F51	Adenoca	Le.Mandible	Simult
Tovi 1984	M33	Follic	Le.Mandible	10 yrs
Markitziu '86	F69	Papill.	Le.Mandible	2 yrs
Hadar 1987	F65	Anaplast	Le.Tonsil	18 mo
Kahn1989	F82	Follic	Ant.Mandible	29 yrs
Whitaker '93	M87	Follic	Tongue Lip	15yrs(°)
Mochimatsu'93	F77	Papill	Tonsil	??
Ferrario 1995	M47	Papill.	Ri.Tonsil	Reveal.
Vural 1998	F64	Follic	Ri.Mandible	18mo(')

(°) debatable case to differentiate from lingual thyroid
(') long-standing goiter

Another group had metastases in the oral cavity, with tongue or mandible involvement (table 13.73).
A M65 presenting with a bulging right palate and lateral pharyngeal wall due to a prevertebral mass was found to have nodal metastases from an unknown papillary thyroid carcinoma (DiLeo et al,). A similar case was reported by Carter et al. in a F53, in whom only a small (1cm) papillary thyroid carcinoma was disclosed.

Ophthalmic Metastases

Metastases to the eye from thyroid cancer would appear to be relatively infrequent, in view of the rare reports published. Remark the proportionally high number of iridial metastases (table 13.74).

Table 13.74 - Carcinoma of the Thyroid Gland
Ophthalmic Metastases Reported

Author	Pat	Histol	Site	Interval
Hornblass '87	F35	'Colloid'	Ri.Orbit (')	6 yrs(°)
Slamovitz'79	F57	Follic	Ri.Choroid	5 yrs
Weisenthal'89	M82	Follic	Le.Iris	(no data)
Bernstein'90	F56	Follic	Ri.Orbit	Reveal
Anteby 1992	F55	Papill	Le.Choroid	8 yrs
Ainsworth '92	F38	Follic	Ri.Iris	7 yrs
Lommatzsch'94	F20	Follic.	Li.Iris	4 yrs
Abarca 1999	M38	Papill	Le.Choroid	4 yrs
Ritland 1999	F80	Follic	Le.Choroid	20(?)yrs
Daumerie2000	F59	Follic.	Le.Orbit	Reveal

(') with important destruction of lateral wall
(°) long-standing goiter

Of seven patients who died with cerebral metastases, two also had orbital metastases as was reported by Tollefsen et al.
Metastasis to ocular muscle (medial rectus) was reported by Friedman et al. in a 72 year-old man, 8 months after the diagnosis of a metastatic thyroid carcinoma of the follicular type.

Cardiac Involvement

Thyroid cancers rarely involve the heart or pericard. A few peculiar cases have been described (table 13.75).
Haskell et al. have reported in a series of 8 patients with a revealing cardiac tamponade, one case of 'adenocarcinoma' of the thyroid in a F44, associated with pulmonary metastases.
Some particular cases of tumor thrombus starting from the thyroid towards the right atrium have been reported Virtually all present with superior vena cava obstruction. Three such cases were reported by Niederle et al. They found 9 other cases in the literature. Since then, apparently no other report on this condition has appeared (fig. 13.25).
Peculiar is that all except one of these patients had no other distant metastases, although some primaries were locally extensive and invasive and associated with cervical nodes. In one patient, the thrombus reached the ventricular outflow.

Table 13.75 - Cancer of the Thyroid
Cardiac Involvement

Author	Pat	Histol	Site	Interval
Clare 1991	F71	Follic	'Card.muscle'	12 yrs
Murabe 1992	M61	Anapl	Ri.Ventricle	Simult
Religa 1996	M40	Follic	Ri.Ventricle	Reveal
Kasprzak '96	M40	Follic	Ri.Ventricle	Reveal
Chiewvit 1998	M62	Follic	Pericard	Reveal
Larsimont'98	M69	Papill	Ri.Ventricle	4 mo
Larsimont'98	M70	Papill	Myocard mult.	1 mo
Bussani 1999				
Kim 2000	F57	Hürthle	Several RA.RV	3 mo

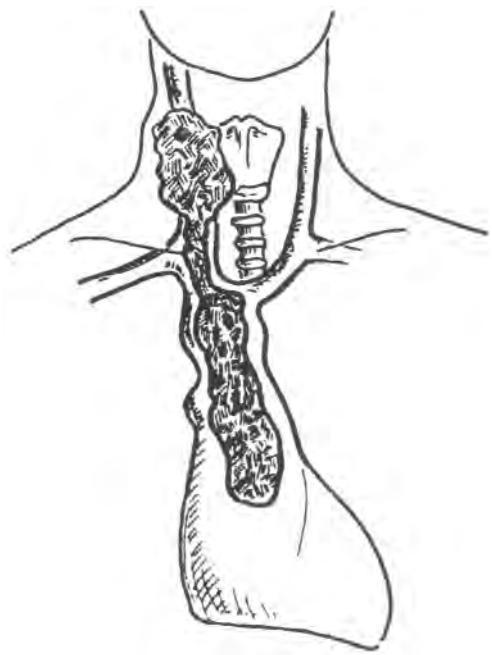

Fig.13.25 - Illustration of the tumor thrombus extending from the right thyroid lobe to the right atrium (Niederle et al., with permission).

Perez et al. reported on a patient (F48) presenting with a thyroid tumor extending from the right lobe retrosternally within the vena cava superior, without the syndrome

Skin Metastases

Metastases to the skin are relatively rarely reported compared to the number of cases of thyroid cancer. The follicular type is particularly prone to this metastatic site. A number are revealing (type 1) metastases although some patients have a history of a long-standing 'benign' goiter.

A typical feature is the violaceous hue observed in several reports, probably a vascular-caused structure. Most will be single metastases, but in a few patients multiple small lesions have been described either at one site or at multiple sites. Many patients will be found to have simultaneous metastases elsewhere or soon after first treatment.

A review of the literature up to 1990 retrieved 40 cases (Roller et al.). Female patients were in the majority with 23 cases, while in 8 gender was not mentioned! Table 13.76 shows a F/M ratio of 2:1 and 18 or 60% cases with metastases to the scalp, accounting together with the neck and face localisations for about three quarters of all reported cases.

Multiple cutaneous and subcutaneous metastatic nodules appeared in a M53 two years after surgery, over the scalp, the face and the trunk. It concerned a follicular thyroid carcinoma (Hamilton).

Reporting on a patient (F40) with multiple cerebellar metastases, Isoda et al. mentioned that the patient had also several cutaneous masses distributed over the anterior trunk.

Table 13.76 - Cancer of the Thyroid
Reported Skin Metastases

Author	Pat	Histol	Site	Interval
Barr 1974	F64	Anapl.	Breast	Autopsy
Taniguchi'96	M61	Anapl	Trunk	2 mo
Dahl 1997	F51	Anapl	Scalp	6 mo
Runne1976	F74	Follic	Epigastrium	6 yrs
Auty 1977	M41	Follic.	Scalp(')	4 yrs
Rico 1985	F78	Follic	Cheek	9 yrs
Pitlik 1983	F26	Follic	Chest wall	5yrs ANTE
Tronnier '91	F53	Follic	Ri.Neck	8 yrs
Tronnier '91	F66	Follic	Scalp Occ.Par	Reveal
Carsuza '92	M76	Follic	Chest wall	Simult
Vives 1992	F71	Follic	Scalp Pariet	9 yrs
Caron 1993	M65	Follic	Scalp Temp.	Reveal
Ehrenschu '93	F57	Follic	Scalp (2)	5 yrs
Toyota 1994	M72	Follic	Scalp	1 yr
Lissak 1995	F79	Follic	Scalp Pariet	Reveal
Lissak 1995	F58	Follic	Scalp Occ.Par	Reveal
Dahl 1997	F43	Follic	Back	19 yrs
Prasoon '98	F55	Follic	Scalp	Reveal
Prasoon '98	F80	Follic	Scalp	Reveal
Cariou 2000	F57	Follic	Scalp	8 yrs
Runne 1976	F29	Mixed	Perineum	6 mo
Horiguchi '84	F70	Mixed	Widespread	11 yrs
Koller 1998	F81	Mixed	Scalp Pariet	Reveal
Horiguchi '84	M62	Papill	Scalp	3 yrs
Doutre 1988	F59	Papill	Scalp(3)	8 yrs
Elgart 1991	M59	Papill	Scalp Pariet	3 yrs
Makris 1996	M70	Papill	Scalp	3 yrs
Dahl 1997	F64	Papill	Neck chest	4 yrs
Dahl 1997	M63	Papill	Scalp chest	7 yrs
Dahl 1997	M47	Papill	Scalp face	16 mo
Loureiro '97	F49	Papill	Thigh Epigastr	4 yrs(')
Abarca 1999	M38	Papill	Scalp (2)	4yrs
Dahl 1997	M33	Medull	Trunk neck	18 mo

(') more skin metastases in evolution

Metastases to the Kidney

These appear to be very rare. Only a few cases have been reported in the (available) literature (table 13.77). Peculiar is that except for two bilateral cases, all are in the left-sided kidney, with a large majority of female patients.

The case reported by Ro et al. showed an hyperdensity on enhanced CT, an uncommon presentation for a renal metastasis. It was avascular on angiogram. The presence of iodine in the follicular carcinoma could explain this unusual density.

Table 13.77 - Cancer of the Thyroid
Renal Metastases reported

Author	Patient	Histol	Site	Interval
Takayasu 1968	F44	Follic	Bilateral	3yrs
Davis 1979	F49	Follic	Bilateral	18yrs
Johnson 1985	F66	Follic	Le kidney	37yrs
Tur 1994	F72	Follic	Ri.kidney	20yrs
Graham 1995	M75	Papill	Le.kidney	Reveal
Ro 1995	F47	Follic	Ri.kidney	7yrs
Lam 1996	F91	Follic	Le kidney	Autopsy
Gamboa 1999	F50	Papill	Le kidney	Reveal
Garcia 1999	F65	Follic	Le kidney	no data
Benchekroun '99	M56	Papill	Le.kidney	3yrs

Bone Metastases

Several small series have been reported, as well as a number of patients presenting first with bone metastasis.

The data of Hermann et al. are the most complete as far as demographic aspects and localisation are concerned. In 151 patients with distant metastases of any kind, there were 56 with any bone metastases, 22 of whom had no other metastases (table 13.78).

It will be noticed that more than 80% concern sites of the upper half of the body. This can only be explained by some venous reflux through collaterals before the circulation joins the superior vena cava.

A further illustration of this are the data of Bru et al. (fig. 13.26). They looked for metastases in the different vertebrae. As one can remark, there is a cluster in the upper half of the spine and one in the lower. We need more data to allow more valuable conclusions, but it but it would appear that a circulation factor is involved. Of the 46 metastatic sites, there were 5 lumbar, 6 pelvic and 4 femoral localisations, or 15/46 (32%) 'below diaphragm'.

Table 13. 78 - Cancer of the Thyroid
Distribution of Bone Metastases(N=56)
Data of Hermann et al.

	N	Sole	All
Skull	19	4	22.6%
Vault 15, basis 4			
Spinal Column	32	5	38.1%
Cervical 2, thorac.18, lumbosacr 12			
Ribs	9	1	10.7
Sternum	6	0	7.1
Humerus	4	2	4.8
Scapula	2	--	2.4
Clavicula	1	--	1.2
Pelvis	9	--	10.7
Femur	2	--	2.4
Total	84 sites	12	

MacCormack et al. (1966) reported on the bone metastases in 33 patients, with 64% above the diaphragm. Recently, Pittas et al. reported on the anatomic distribution of bone metastases in 146 patients (table 13.79). Unfortunately, the data on the spine were not given accordingly to the segment. They state that in half of the cases the bone metastases were present at first diagnosis. A number (no data) presented with symptoms of bone metastases first.

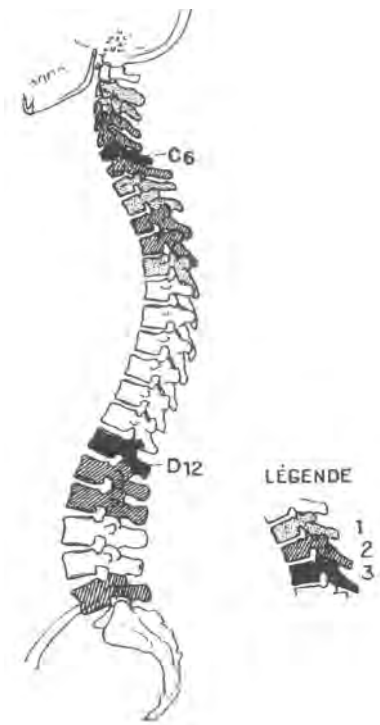

Fig.13.26 - Distribution over the various vertebrae of 27 metastases in 11 patients (from Bru et al.)

Table 13.79 - Cancer of the Thyroid
Distribution of Bone Metastases (N=146)
Data of Pittas et al.

Skull	13%	Pelvis	50%
Vertebrae	54%	Femur	21
Ribs	31		
Clavicle	5	Other(')	5
Scapula	3	Multiple	54
Manubrium	4		
Humerus	11		

(') includes radius, shoulder, tibia, fibula

New data have recently been reported by Tickoo et al. on 79 cases. In 40, the metastases were found at the diagnosis of the primary, including 24 symptomatic and 16 at staging. During follow-up 39 more were found, of which 66% in the first year. More data are in table 13.80. The number of treated patients and the site of the metastases were not reported.

The data on the symptomatology of bone metastases in thyroid cancer are interesting (table 13.81). In one quarter, the metastases were asymptomatic.

Table 13. 80 - Cancer of the Thyroid
Bone Metastases (N=79)(')
Data of Tickoo et al.

Histology	M:F	Symptomatic	Staging	Follow-up
Follicular	10-7	6	6	5
Papillaty	10-12	5	2	15
Hürthle	6-3	3	0	6
Insular	10-6	5	4	7
Anaplastic	4-6	3	5	2
Medullary	1-4	2	1	2
Total	41-38	24 (30%)	16 (20%)	39 (49.3%)

(') 40 at diagnosis, 39 during follow-up

Table 13. 81 - Cancer of the Thyroid
Symptomatology of Bone Metastases (N=146)
Data of Pittas et al. (2000)

Asymptomatic	22.9%	Swelling	11.1%
Pain	50.7%	Fracture	4.9
Unclear	8.3%	Spinal Cord Compression	3.5%

It would appear that there is a need for more detailed reporting, in spite of the fact that this may seem irrelevant for evaluating treatment results. In a series of 37 surgically treated vertebral metastases from thyroid cancer had there were 4 cervical, 18 thoracal, 10 lumbar and 5 sacroliac bone metastases.

A few cases presenting with spinal cord compression have been reported. Two concerned the cervical region (Goldberg et al.), both from a follicular cancer and one at T-10 level from a mixed papillary-follicular carcinoma (Goldstein et al.). A literature review by the first author disclosed 4 other cases. All concerned cervical or thoracal vertebrae and only one at L2. Another case at the level of T2-T3 was reported by Shortlife et al., while Tovi et al. described one case with a posterior mediastinal mass which had invaded three vertebrae and further spread into the intraspinal contents. A similar case (F74) was recently reported by Zeidman et al., where the metastases at T7-T10 was the revealing symptom.

Symptoms from invasion into the base of the skull with progressive extension of the symptomatology prompted a MRI of the skull base revealing a chordoma-like image at the clivus. Biopsy disclosed a follicular carcinoma metastasis. It was the only metastatic site in this M61 and a small (0.9 cm) tumor was found in the thyroid (Casals et al.).
An occipital skull metastasis invading the brain and the subcutaneous tissue had evolved to a seizure symptomatology in a F75. Biopsy showed a papillary thyroid carcinoma, the primary being a small focus of 1 cm in the right lobe (Lin et al.).

Quite a number of patients with a revealing osteolytic metastasis associated with some tissue-mass have been reported. One was reported by Boehm et al. and three cases described by Kearns et al. In all patients, a follicular thyroid cancer was found. A solitary metastasis in the clavicula was found simultaneously with

the diagnosis of thyroid cancer of the insular - a variety of follicular - type (Bose et al.).

Another uncommon feature is the relatively high incidence of sternal involvement compared with other cancers. Of 77 cases with sternal metastases, 14 or 18% originated from a thyroid cancer. Remember that breast cancer is the major primary site, in this series accounting for 52%. In the other small series on sternal metastases, there are always some thyroid cancers included. Local venous reflux might be connected with this particular metastatic site.
A particular and rare form of thyroidal metastasis at the sternum is the pulsating form. The abundant vascularity of the metastasis predisposes for shunting between arterial and venous resulting in a pulsating tumor. A few from the thyroid have been reported (Estrera et al.). A case reported by Sand et al. was interpreted finally as resulting from an ectopic mediastinal thyroid. An illustrative case taken from our own files is shown in fig. 13.27.

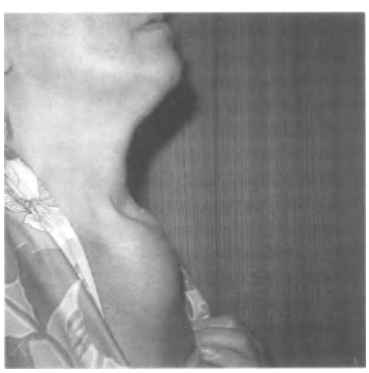

Fig.13.27 - Metastases in the Sternum occurring 2 years after surgery for a follicular thyroid carcinoma.

An acral metastasis in the left ring finger was reported in a women (F64), 5 years after thyroidectomy for a follicular carcinoma (Uriburu et al.). A peculiar case was reported by Giraud et al. A F60 presented with pain in the left thumb. Radiology revealed a destructive osteolysis and surgery disclosed follicular thyroid carcinoma, which was confirmed. Some three months later, widespread metastases were found.
In describing a case with mandibular metastasis (see above), Kahn et al. mention a metastasis in the tibia and in the pelvis in the same patient.

Reporting on a case of medullary thyroid cancer to the temporal bone, Redleaf et al. mention that the literature should contain only 10 cases, of non-medullary thyroid cancer. The review covered the period 1922 to 1985.

Bone marrow metastases have been the subject of a few reports. In 62 patients the bone marrow was explored with scintigraphy and/or MRI. The findings were normal in 34 patients, but there was suspicion in only 8 patients. Pathological radio-iodine uptake was seen in only 4 while in 2 it was assumed due to serum-thyreoglobulin increase. A few other series have mentioned an incidence of 3% bone marrow involvement.
In fact, every patient in whom there are radio-iodine concentrates in the long bones must be suspected for bone marrow involvement. An exceptional case was reported, where bone-marrow biopsy indicated for staging of a malignant lymphoma, disclosed a metastatic follicular thyroid carcinoma as a second primary (Vassilopoulou-Sellin et al.).

Liver Metastases

Metastases to the liver are relatively rare for thyroid cancer. No systematic study addressing this site is known. They account for about 1% of the patients with metastases. Most have been detected with radio-iodine surveys as cold zones (Atlmaran et al.) and even as hyperactive focus of hyperthyroidism of an unknown cancer (Studer et al.).
Tur et al. have reported on a woman (F72) presenting 20 years after first treatment with a huge liver metastasis in the caudate lobe, simultaneous with one in the kidney.

Diffuse liver uptake with I-131 may be indicative of a functioning thyroid remnant or metastases or can suggest hidden metastases (Chung et al.).
Abdominal CT revealed diffuse hepatic metastases in a patient M55 with a known thyroid cancer. Imaging was prompted by Cullen's sign presenting, or periumbilical ecchymosis (Marinella).

Other Metastases

Twelve years after left thyroid lobectomy for follicular carcinoma, a patient (M65) presented with left flank pain and shoulder arthralgia. Eventually, a large splenic mass was observed with vast infiltration of the diaphragm, the stomach, the colon and the pancreas (Paolini et al.).

A subcutaneous scapular mass in a F58 was the revealing situation of a follicular thyroid carcinoma (Sevinc et al.).

According to Lee et al., reporting on a papillary thyroid cancer metastasis to the mid-esophagus (M68), five other cases have been reported, but some without histological confirmation. They must be differentiated from the more frequent contiguous invasion. Such a case was reported by Cooney et al. in an 81 year old woman, though this is not an uncommon situation.

We are aware of two patients in whom pituitary metastases developed with panhypopituitarism both from a papillary thyroid carcinoma, one 14 years (Johnson et al.) and one 25 years (Sziklas et al.) after first surgery.

In a series dealing with adrenal tumors complicated by caval thrombus, Peix et al. mention a patient (F82) with an adrenal metastasis from a thyroid cancer, without giving any further details.
Metastases in the breast, as distinct from cutaneous metastases, have been reported, one even as first sign (table 13.82).

Table 13. 82 - Carcinoma of the Thyroid
Breast metastases - Cases reported

Author	Pat	Site	Histol	Interv.
Ascani 1994	F57	Le.breast Upp.Ext.	Follic	Reveal
Loureiro '97	F49	Ri.breast	Papill	14 yrs
Fiche 1998	F59	Ri.breast Upp.Ext	Papill	2 mo

A patient (F66) presented with a long history of chronic abdominal pain radiating to the back. Eventually, a CT showed a mass consistent with an abdominal aortic aneurysm. A thyroid nodule was palpable but judged benign. Finally, a laparotomy disclosed retroperitoneal massive lymph nodes necessitating extensive vascular surgery. At histology anaplastic thyroid carcinoma was described, confirmed at autopsy (!) similar to that of the thyoid nodule (Lip et al.).
About 2 months after thyroidectomy, a patient (F66) had to undergo laparotomy because of intestinal obstruction. Four discrete masses involving the small intestine were identified, some fixing the loops together. Other metastases were found in the omen-tum. Two months later, a generalization within the abdominal cavity occurred (Phillips et al.).

Six months after radical thyroidectomy for a tall cell papillary carcinoma, the patient (M53) presented with abdominal pain. A mass in the head of the pancreas was seen at CT, but at laparotomy multiple nodules were identified, as well as several peripancreatic metastatic nodes (Jobran et al.).

Adrenal metastases are very rare in thyroid carcinoma. Orsolon has reported a case (F66) in an Hürthle carcinoma associated with several other metastases, and Blanchet et al. reported on two cases where the presence of adrenal metastases was detected at first diagnosis. Only one other patient is claimed to have been reported (Girelli et al.). In their series of patients with caval vein tumor thrombus, Peix et al. mention one patient with a solitary adrenal metastasis occurring 25 years after first treatment for a differentiated thyroid cancer. Further details were not given.

Hyperthyroidism - Hyperfunctioning Metastases

Symptoms of hyperthyroidism in thyroid cancer can occur in different situations. It always involves a hyperfunctioning activity or overproduction of thyroid hormone by a differentiated tumor.
It can occur as first - presenting- symptom of an unknown thyroid cancer, either as a hyperactive toxic nodular cancer, or due to a hyperfunctioning metastasis, as revealing symptom. Hyperfunctioning metastasis occurring during follow-up is the other possi-bility. An extensive classification of the association between hyperthyroidism and thyroid cancer has been formulated by Salvatori et al. (table 13.83).

Several case reports of both situations have been published. We have collated the reports available to us (table 13.84).

Of a cohort of 125 patients with differentiated carcinoma, 35 showed evidence of distant metastases and in six of them, the metastases were considered to produce thyroid hormone. This gives an insight into the incidence, with the bias, however, that these patients originated from a 'goitrous' area of Brazil (Gross et al.).

Table 13.83 - Cancer of the Thyroid
Associations with hyperfunctioning metastases
Classification by Salvatori et al.

1. Incidental Papillary Cancer
   Hyperthyroidism through stimulation of tumor
2. Incidental microscopic papillary Cancer
   Multi-nodular goiter with hyperfunction
3. Incidental Follicular Cancer
   Multi-nodular goiter with hyperfunction
4. Metastatic thyroid cancer
   Hypersecretion of hormone from metastases in bone, lung, lymph nodes and other.
5. Struma Ovarii (benign, malignant or metastatic)

Table 13. 84 - Cancer of the Thyroid
Cases with hyperfunctioning metastases
Revealing cases

Author	Pat	Site of Metastasis	Histology
Hunt 1960	F61	Lung Bone	'Carcinoma'
Ginsburg '63	F62	Femur fracture	Follicular
Shahani 1967	M65	Hip joint	Follicular
Ghose 1971	F68	Skull metastasis	Mixed hist.
Sung 1973	M52	Several Vertebrae	Follicular
Kruter 1981	F50	Skull metastasis	Follicular
Chapman '84	F70	Lung-Bone	Follicular
Bowden '86	M65	Several Vertebrae	Follicular
Scheübl '89	M74	Diffuse Lung	Follicular
Jortay 1994	M82	Iliac - Tox.Nod.	Follicular
Barrande '97	M35	Toxic nodule	Follicular
Barrande '97	F57	Toxic nodule	Papillary
Cirillo 1998	F17	Toxic nodule	Papillary
Appetecchia'98	M23	Toxic nodule	Papillary

The data in table 13.85 show that almost all cases with distant metastases and hyperthyroidism, had a follicular cancer, with a large majority of female patients. Most have a long-standing goiter, nodular or not.

As far as the hormonal products are concerned, Kasagi et al. have identified two features. An excessive thyroid hormone (T4) production by a large amount of meta-static tumor tissue is the most frequent situation. Only 4 cases with T3-toxicosis should have been re-

ported. It concerned the cases reported by Sung et al., Snow et al., Nakashima et al. and Kruter et al. To these should be added the case reported by Kasagi et al. and the one by Yeo et al. In some cases, the biochemistry may be more complex, with the presence of TSH-receptor antibodies, TSH-binding Immunoglobulin Inhibitor and Thyroid-Stimulating antibodies (Kasagi et al.).

Table 13. 85 -Cancer of the Thyroid
Cases with Hyperfunctioning Metastases

Simultaneous				
Valenta 1970	F58	Follicular	Pelvic	Simult
Valenta 1970	M60	Trabecular	Lung mult	Simult
McConnon '75	M45	Follicular	Pleura	Simult
McLaughlin'70	F70	Follicular	Lungs	Simult
Steffensen '94	F71	Follicular	Lung	Simult
Salvatori '98	F79	Follicular	Lungs	Simult
During Follow-Up				
Studer 1961	M13	Langhans(')	Liver	10 yrs
Valenta 1970	F49	Follicular	Pelvic	8 yrs
McLaughlin'70	F56	Follicular	Femur	1 yr
Daumont '77	F64	Follicular	Liver-Bone	8 yrs
Grayzel 1979	F39	Follicular	Lung	9 yrs
Nakashima '81	F53	Papillar	Lung	3 yrs
Kasagi 1994	F76	Follicular	Bone diff	5 yrs
Kasagi 1994	F67	Follicular	Bone diff	1 yr
Kasagi 1994	F48	Follicular	Lung	1 yr
Ikejiri 1997	F59	Mixed histol.	Bone	20 yrs
Kobayashi '97	M52	Follicular	Diffuse	5 yrs
Salvatori '98	F69	Adenocarc.	Lung	25 yrs

(') Langhans tumor

Imaging Particularities

While current imaging methods such as conventional X-rays, US-graphy and CT are of importance in the diagnosis of metastases, as they are for all other cancers, nuclear scintigraphy plays also an important role, even more than in the era of radio-iodine, as many other tracers have been developed.

In spite of some inherent disadvantages including the high energy gamma-rays and their relatively long biologic half-life in some particular situations, **Iodine-131** still plays a major role. **Iodine-123** may be a good alternative in some situations, but is more expensive.

Not all metastases will capture iodine, as has been shown in pulmonary and other locations, probably due to the central necrosis.

Other radiopharmaceuticals have been investigated such as **F-18-deoxyglucose** (FDG), **thallium-201** chloride, **Tc-99m-sestamibi, Tc99m-tetrofosmin** and **Ga-67** citrate.

Reviewing 99 consecutive patients evaluated with whole-body **Tc-99m-sestamibi,** Almeida-Filho et al. concluded that the tracer is very valuable in the follow-up of differentiated thyroid carcinoma, particularly when thyroglobulin is abnormal and after a negative **I-131** scan. Sestamibi and tetrofosmin pharmaceuticals with their high affinity to mitochondria, are likely to be most useful in mitochondria-rich tumors such as the Hürthle-cell cancers. However, the high uptake in heart, liver and bowel will limit their sensitivity for detecting thoracal metastases.

The high sensitivity of **F18-FDG** is dramatic especially in cancers thet have become less differentiated and more aggressive due to a higher metabolic rate. According to Jana et al., it might be useful specifically in patients with high Thyreoglobulin and a negative iodine-scan, as in anaplastic and medullary cancers.

Prospective studies have shown that within the same patients, some metastases can be visualized only by I-131 and others only by FDG, illustrating the diversity in metastatic populations that can exist in every cancer patient. This has been called a 'flip-flop' phenomenon (Feine et al.).

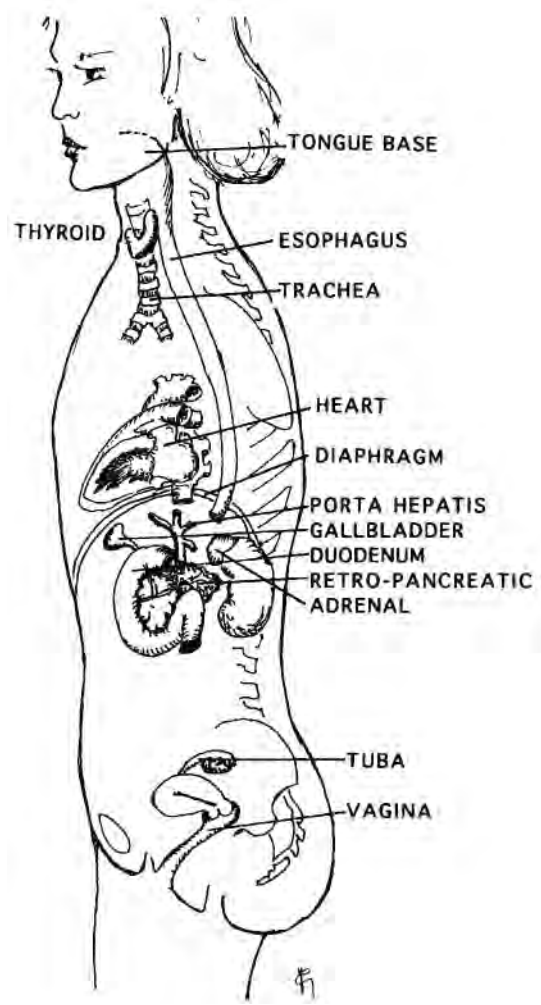

Fig.13.28 - Sites reported to occasionally contain ectopic thyroid tissue.

Differential Diagnosis

We think it important to mention that at least for radio-iodine nuclear scintigraphy, the possibility of ectopic thyroids must be taken in account. They are

well-known in the tongue and along the embryologic site of the thyroglossal duct, but have been described in the mediastinum, the heart and very occasionally in the abdomen (fig. 13.28). Furthermore sites or pathological conditions where non-cancerous iodine uptake can be observed, must be taken in account. This has extensively been reviewed by Bakheet et al. and Mitchell et al.

Tumor Markers

Serum levels of thyroglobulin can be used to monitor the treatment and detection of recurrences in well-differentiated thyroid cancers. The levels will be normal or low in patients with anaplastic or medullary cancers. They are not helpful for the differentiation of benign from malignant nodules. In follicular carcinoma, the level normalizes after surgery but can rise in the event of recurrence or metastases. Other non-cancerous conditions may have elevated levels, however.

Causes of Death

As the majority of differentiated thyroid cancers are cured by the first treatment, causes of death actually apply only for locally progressing or metastatic disease. Local problems are the main cause of death as inva-sion of the upper airway and of the esophagus, the vascular structures will be frequent and often extensive, but also pulmonary metastases, or secondary pneumonia (table 13.86).

Table 13.86- Cancer of the Thyroid
Papillary Cancers - Causes of Death(N=56)
Data of Smith et al.

Local Evolution	36%
Neurological	21%
Hemorrhage	2%
Pulmonary	37%
Unknown	4%

Recently, an extensive report on 161 fatal cases was published by Kitamura et al. Respiratory insufficiency was the most common specific fatal condition, followed by circulatory failure, hemorrhage and airway obstruction. The previously reported data of Silliphant et al. are also in table 13.87.

Respiratory insufficiency may have various different causes. Diffuse and extensive lung metastases replacing a large amount of lung tissue, massive hemorrhage and massive airway obstruction caused by uncontrolled local tumor or circulatory failure resulting from vena cava compression by extensive mediastinal or sternal metastases were the most important cause of death.
Distant metastases either with or without local recurrence occurred in 61% (table 13.87). The authors have also analyzed the data according to histology (data not shown), but no particularly significant differences could be observed.

Table 13. 87 - Cancer of the Thyroid
Specific Causes of Death

	Silliphant N=94	Kitamura N=161
Respiratory Insufficiency	82%	43.4%
Circulatory Failure	--	15.1
Hemorrhage from tumor	6%	15.1
Airway Obstruction	26%	13.2
Other(')	15%	13.2
(') including 2 brain metastases		
State of tumor at death		
Local lesion alone	--	34.8%
Local and metastatic lesions	--	28.0
Distant metastasis only	17%	33.5
Other complications	--	3.7
Metastasis present		
Pulmonarymetastases	--	77.5%
Bone metastases	--	27.5

METASTASES from MEDULLARY THYROID CANCER

The medullary type of thyroid cancer (MTC) presents either as a sporadic entity or as part of different familial syndromes. The reader is referred to other reviews for discussion on the subject.
The metastatic distribution of this type of cancer is somewhat different from the previously discussed histological types. In common however, is the aggressive local and regional spread, especially as far as lymph node metastasis is concerned.

Local invasion within the pharynx and larynx has been reported in a few cases (Thinakkal et al. and Sweeney et al.).

Lymph node metastases will be frequent and often extensive, where the most frequently involved level is mid- and lower jugular, up to 75% of the patients (Ellenhorn et al.). The mediastinal nodes seem to be metastatic in 50% of the patients.

Imaging

Classical X-rays, CT and MRI play an important role in the delineation of the extent of this aggressive tumor. Radio-iodine (NaI) scintigraphy is, however, of no use. Scintigraphic studies have been performed with Thallium-^{201}, Tc^{99m}-DMSA, I^{131}-MIBG, Tc-^{99m}-MIBI, labeled anticalcitonin and anti-CEA-antibody (review by Juweid et al.) though with limited sensitivity and inadequate specificity, although reports of successes in particular cases have appeared (Hocate et al.).
The recently introduced Somatostatin Receptor Scintigraphy, although indeed aspecific for 'screening' as the tracer is taken up by a variety of tumors, seems very useful in the detection of metastases if used in

addition to CT (Berna et al. and Krausz et al.).
A study by Adalet et al. concluded that the different radiopharmaceuticals were complementary due to their different sensitivities for the different tissues. DMSA has a high affinity for lymph node, pulmonary and bone metastases, while the uptake of the other tracers was somewhat variable.
Recently however, F-18-dihydroxyphenylalanine PET has been introduced and should be very promising and have better results than SRS and FDG (Hoegerle et al.).

Diagnosis of Metastasis

Apart from use in the clinical and imaging evaluation of the patient, serum calcitonin plays an important role in the diagnosis, screening and in the evaluation of treatment response, but also in early warning of tumor recrudescence. Fine Needle Aspiration cytology and biopsy is as helpful as in other cancers.

Distant Metastases - Autopsy Data

A few reportsprovided data on the metastatic spread in patients dying from their cancer. A striking difference with the differentiated cancers is the much higher rate of liver metastases (table 13.88).

Table 13.88 - Medullary Carcinoma of the Thyroid
Distant Metastases - Autopsy Data

Site	Williams 1966 N=20	Gordon 1973 N=40	Rasmusson 1984 N=14
Nodes	13	30	3
Mediastinum	--	11	4
Lungs	9	4	5
Pleura	2	--	--
Heart	1	1	--
Liver	5	3	5
Bones	4	9	4
Adrenals	4	--	--
Ovary	1	1	--
Pancreas	1	3	--
NONE	4	--(')	--(")

(') 1 in gallbladder, ileum, omentum, bile duct, brain, trachea, paraaortic nodes.and 2 with axillary nodes
(") 1 skin, breast, uterus, prostate, kidney, retroperitoneum, abdominal nodes

Table 13.89 - Medullary Carcinoma of the Thyroid
Distant Metastases at presentation
Data of Delisle et al.

	Solely	With other
Present in 25 patients		
Nodes (Non-Cervical)	5	6
Lungs	4	7
Bone	3	8
Liver	1	4
Other	2	1

More interesting are the extent of metastasis at diagnosis. This has been discussed by Delisle et al. They noted that in 7% of the 117 patients a metastasis was the first sign. Metastases were present in 25 patients or 21%, illustrating the aggressiveness of this type of cancer, or the possibility of a late diagnosis (table 13.89). The literature on distant metastases from a medullary thyroid cancer is mainly made up of several case reports, except on liver metastases.

Liver Metastases

As shown on the autopsy data, the incidence of liver metastases is much larger than for the differentiated cancers. At autopsy, they will be found in about 25% of the patients.
Metastases to the liver can consist of either one or more large nodules, but in other cases, it can almost replace the whole liver (case of Dubé et al.).
A prospective study in 13 patients disclosed the presence of liver metastases in 3 patients or 23%.

The echographic aspects of liver metastases in MTC have been studied by Leclère et al. They identified four types, small nodules without peripheric halo, micronodular and strongly hyperechoic, nodules larger than 3cm and hypo-echogenic, sometimes with central necrosis. Of the 35 patients, 13 (37%) had a mixed type, the larger nodules being the least frequent.
At CT, the liver metastases appear as solid sometimes calcified, masses or small round calcifications without a definite mass. Two cases with multiple calcified lesions within the liver associated with calcified hilar nodes were described by MacDonnell et al. At MRI the solid masses are readily viewed, but calcifications can escape attention, unless the appropriate technique is used.

A series of 41 patients with recurrent thyroid medullary carcinoma underwent laparoscopy or direct biopsy. Liver metastases were found in 8 or 19% (Tung et al.). In seven patients, the metastases were not visible either at CT or MRI. Unfortunately the authors did not mention the location of the metastases. One laparoscopic image is shown where small metastases are visible at the surface of the liver, probably microseedings as a number of patients had apparently previously abdominal surgery. This confirms that there is an urgent need for uniform reporting of the type of liver metastases.

Bankoff et al. mention the occurrence of multiple calcified lesions in the liver associated with similar lesions in the spleen, 'several years' after surgery for a MTC in a F30. Biopsy confirmed metastatic lesions in both organs.

Other Metastases

Brain metastases would appear to be very rare. According to Pitale et al. reporting on one case (M43), only six other cases have been reported. Their patient had

two cerebral locations associated with multiple small cerebellar foci, a rare metastatic situation. Pre-viously, Timothy et al. reported on a F67 who presented 3 years after surgery with manifest ataxia, leading to detection of one large lesion in the cerebellum.
In the series of 47 patients with brain metastases, Chiu et al. mention 4 cases with MTC, of which 3 were only found at autopsy. Site wa,s however, not reported.

Months after having been shown to have pulmonary metastases, a large liver (10 cm) was found in a M24 complaining of nausea and headache. An intrasellar mass was seen at MRI, confirmed by transsphenoidal biopsy to be metastatic from a MTC (Dempsey et al.).

Four cases of metastases to the breast should have been reported (table 13.90).
Kumar et al. mention one patient with metastasis to the uterus in their series of 63 patients with metastasis to this site.

Table 13.90 - Medullary Carcinoma of the Thyroid
Breast metastases reported

Ordonez 1988	F72	Ri. Upper half(°)	22 yrs
Ahuya 1991	F47		21 yrs
Kiely 1995	F64	Le Upp.Out.Q.	2 yrs
Scott-Soo 1995	F40	Le.Upp.Out.Q	7 yrs

(°) two years earlier also various skin metastases

A few reports concerning bone metastases have been published. Reyes et al. have reported on a patient with diffuse mixed osteoblastic and osteolytic metastases. After reviewing 70 patients with MTC, Wallace et al. stated that the bone metastases are invariably osteolytic with no specific identifying features.
A case with an apparently solitary metastasis to the temporal bone in F58 was reported by Redleaf et al. The symptomatology occurred 22 years after first surgery. It would appear to be the only reported case of MTC metastatic to this site.

Overall Lesson

Thyroid carcinoma is, due to its superficial location, readily accessible for clinical examination and early diagnosis. As the large majority of the tumors remain loco-regional, it remains within the boundaries of adequate surgery.
The low rate of distant metastases is a factor in the relative good prognosis, but the various uncommon and sometimes irregularly occurring metastases are again pitfalls for the clinician who is not aware of the possible metastatic locations.

METASTASES from PARATHYROID CARCINOMA

Parathyroid carcinoma is a very rare tumor. Its low incidence means that pertinent data on a metastatic pattern are not available.

Literature reviews show that lung metastases are the most frequent type occuring in about 25 to 35% of the patients. The short follow-up in most case reports does not allow correct incidence data, as several have occurred one or two decades after first surgery. The lung metastases are usually described as multiple, but there have been cases with a single parenchymal metastasis.
Kuhlencordt et al. claim to have treated a patient in whom the pulmonary metastasis was present years before diagnosis of the metastatic parathyroid carcinoma, as it was first considered a tuberculoma.

Bone metastases must be differentiated from osteolytic situations due to the high level of parathormone, though several were confirmed at histology. No preferential site for bone metastases is noticed, but only cases in the axial skeleton have been described. Manente et al. have reported on a patient (F41) where immunohisto-chemical studies indicated the possibility that parathyroid cancer cells where able to secrete both parathormone and calcitonin.

Metastases have also been reported in the mediastinal nodes, in the liver and the pancreas (Obara et al.). A few brain metastases have been reported (Anderson et al.). In one patient of the latter author, mention is made of an axillary node.

METASTASES from RETINOBLASTOMA

Primary malignant tumors of the eye are rare. Only the retinal tumors or retinoblastoma have a frequency large enough to obtain significant data on the incidence of distant metastases.
Retinoblastoma, a rare neuroectodermal tumor, is the most common intraocular malignancy of childhood. The sporadic can be distinguished from the more common hereditary, as well as an unilateral and a bilateral form. An even rarer occurrence is the trilateral form, where the pineal gland is associated in the malignancy process.
According to a number of authors as MacKay et al. and Karcioglu et al., about 10 to 15% will develop a metastasis once, usually within the first year after diagnosis.

Staging-Classification

As far as staging is concerned, the classic Ellsworth-Reese staging does not have a specific stage for metastatic disease. The American Joint committee on cancer keeps it simply to Ml, while the St.Jude's Hospital system adds a stage IV, but divide it in three classes, probably based on prognostic data:

IVa: extension through optic nerve to brain
IVb: blood borne metastasis to any tissue
IVc: bone marrow metastases.

These classifications have not produced data on distribution of other statistics in the literature.

Pathways

When untreated, the tumor evolves to a complete destruction of the eyeball, with possible spread along the optic nerve towards the cranial cavity, but also to neighbouring facial structures. The maxillary antrum is invaded from the orbit.

Data on metastatic pattern are absent in the literature.

An unusual but understandable form of spread, apparently rarely reported, is intradural spread. This occurs probably after invasion of the dura and the meningeal space and is propagated through the CSF. Lipper et al. were able to report on 4 such cases. In three of them the metastases were located low in the lumbar region up to the cauda equina. This situation is a repeat of what we have discussed for some intracerebral primary tumors (Chapter 5). The fact that 4 cases were reported from one institute probably means that it is underreported.

Orbital extension seems to occur in about 10% of the patients, at least as reported by Rootman et al. It presents with proptosis, a palpable orbital mass or lid swelling and ecchymosis, while the tumor may already have spread to the CNS or/and systemically. From histology-studies, they were able to identify three pathways of how the tumor could reach the orbital content (table 13.91) (Fig.13.29). We have summarized the different pathways of spread on table 13.92 (Figure 13.30).

Table 13. 91 - Retinoblastoma
Invasion pathways to the Orbit
Modified from Rootman et al.

1. Via Schlemm's canal and the intrascleral venous plexus
2. Erosion of the tunic
3. Invasion of the ciliary body and egression along the anterior emisssary veins
4. Early extension along emissary in region of vortex vein
5. Egression along posterior emissary from choroid

Table 13.92 - Retinoblastoma
Pathways of distant spread

1. Spread along the optic nerve to the brain
2. Perineural spread along the optic nerve to the dura and meninges, then intraduralyl up to cauda equina
3. Centripetal spread along nervus trigeminus and centrifugal to subcutaneous tissue
4. Invasion of the orbit, towards the maxilla
5. Through peri-orbital veins into the sinus cavernosus and hence to the subarachnoid space
6. Hematogenous (Batson's plexus ?)
7. Lymphatic spread, when orbit is involved

Risk of Distant Metastases

Several authors have attempted to delineate the risk for subsequent metastases and relate it to the pathology of the primary.

Kopelman et al. (1987) were the first to observe a high risk in patients with invasion in the optical nerve or of the orbit. Choroidal invasion was not significant, but they noted that the presence of cataract, bilaterality and 'late diagnosis' were significantly associated. Later in 1991, Messmer et al. noted the four following risk factors: invasion of the optic nerve with or without involvement of the resection line, choroidal invasion and late surgery.

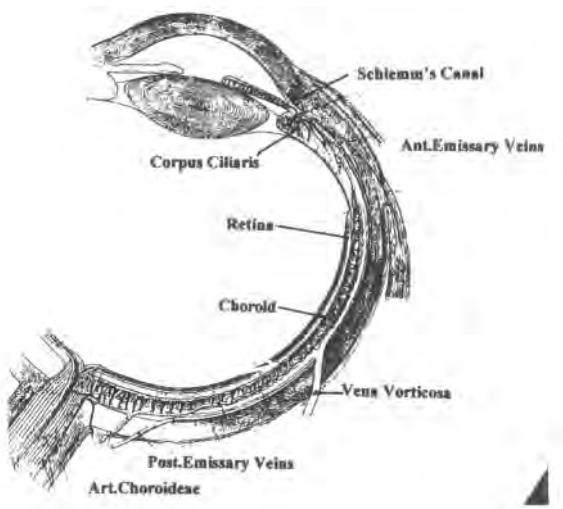

Fig. 13.29 - Structures permitting spread of retinoblastoma towards orbit and central nervous system (see text)

Choroidal invasion was found to be more frequent with increased intra-ocular pressure and iris neovascularisation, optic nerve invasion and poorly differentiated retinoblastoma. Choroidal invasion is a risk factor, certainly when associated with optic nerve invasion. Later, they could add that large exophytic tumors were highly asso-ciated with optic nerve invasion, the main risk factor for metastases. In all these studies however, no attention was paid to the site of distant metastases (Shields et al.).

Site of Distant Metastases

Having treated 235 patients, Gaitan-Yanguas observed distant metastases in vivo in 76 (30%) patients. The series derived from Columbia,S.A., with a high number of advanced cases and patients with limited social possibilities. They classified the metastases according to the side of the primary (table 13.93).

Of 23 cases with metastases, 10 had cranial and 13 cranial and distant metastases, but the sites were not detailed (MacKay et al.). In a series of 261 patients, Karcioglu et al. observed distant metastases in 11.6%

of the unilateral cases and 14.9% in the bila-teral cases. Six had brain metastases, three had bone metastases but only 3 had lymph node metastases. Further details were not provided.

In metastasized cases, about 57% had extra-ocular disease, of which 69% intra-orbital, 39% with a cranio-neuropathy, and involvement of bone marrow in 39%. Ultimately, half of the patients with extraocular disease will later develop invasion of the brain, spinal cord, meninges or epidural space.

Table 13.93 - Retinoblastoma
Extracerebral metastases N=76 of 235
Data of Gaitan-Yanguas

Site	Homolat	Contralat	Total
TemporoOccipital Region	32	12	39
Other cranial nodules	9	4	11
Maxillary antrum	15	2	16
Lymph No Pre-auricul.	16	5	19
Lymph No Cervical	12	0	12
Orbital bone wall	18	0	18
Distant bone			3
Pulmonary metastases			1

Table13. 94 - Retinoblastoma
Distant CNS-Metastases as in 19 Autopsies
Abridged Data of Merriam 1950

Bones around Orbit	6	Intracranial structures		
Invasion of the Nose	3	Optic nerve	10	
Invasion of Mandible	3	Chiasma opticum	9	
Sinuses (any)	3	Arachnoid	9	
Oral Cavity	2	Ventricles	7	
		Cerebral cortex	7	
Lymph Nodes	8	Cerebellum	4	
Cervical	3	Pituitary gland	3	
Hilar	2			
Retroperitoneal	3	Spinal cord	4	
Inguinal	2			

While involvement of the CNS can occur without any other recurrence after treatment, it can occur even later than 2 years after first treatment.

Table 13.95 - Retinoblastoma
Distant Non-CNS Metastases as in 19 Autopsies
Abridged Data of Merriam 1950

Bone		Visceral	
Any Skull bone	9	Liver	5
Ribs	7	Kidney	2
Shoulder	1	Testis	2
Humerus	3	Pancreas	1
Radius Ulna	4	Spleen	1
Vertebrae	5	Ovary	1
Pelvis	4	Uterus	1
Femur	4	Abdom.Muscle	1
Tibia	3	Aorta	1

Half a century ago, Merriam reported a very detailed study of 19 autopsies (table 13.94). Intracranial metastases were present in all but 1 patient. In half of the cases, there was leptomeningeal and subarachnoidal involvement, without involvement of the dura. From the LM on, the invasion had progressed to the cranial nerves. Skull bone was involved in half of the patients, with in some further erosion toward sthe dura and arachnoid. Cerebral cortex was invaded from the LM and further spread towards the brain stem was observed. The data of Merriam are on table 13.95, but in an abridged version of their very detailed report.
These data clearly show the ubiquitous possibility of metastatic spread of such a small but clearly aggressive tumor.

At autopsy, brain parenchymal metastases are reported to be present in 25 to 94% of the patients, depending on the reports. Half of the deaths will be due to CNS involvement (Petty et al.).
The rare 'variety' of hemorrhagic cerebral metastases was reported as occurring in two patients by Atlas et al.
Meningeal dissemination was observed in 8 or 22% of the 37 patients treated (Meli et al.). In two of them, the primary was bilateral. Symptoms were not different from thoise in adults. Diagnosis was obtained at CT, showing meningeal enhancement and ventricular dilatation in most of them. In one patient, multiple intra-dural metastases were also noted.

Table 13. 96 - Retinoblastoma
Metastases depending on involvement
Data of Stannard et al. 1979

	N3 (N=25)	C3-C4(N=21)(')
CNS	14 (87%)	15 (71%)
Local	10 (62.5%)	17 (81%)
Distant	8 (50%)	11 (52%)

(') N3: whole optic nerve is invaded up to section
C3-C4: Invasion of all ocular structures

As far back as 1979, Stannard et al. reported on the differential incidence of distant metastases depending on the invaded part of the eye (table 13.96). Local recurrence was more frequent in C3-C4 patients, while distant metastases showed no difference in incidence. The distant sites were not reported.

Lymph Node Metastases

We are not aware of systematic study of cervical metastatic lymph nodes. Stevenson et al. have reported on a girl with cervical node three months after enucleation. Side was not reported... We have personally treated one patient with bilateral cervical nodes.

Metastases to the Oral Cavityy

A frequent metastatic site is the oral cavity. A number of isolated cases have been reported (table 13.97).
The pathway to the mandible is more difficult to explain. As most had metachrone localisation, a possible explanation is initial centripetal perineural spread along the nervus trigeminus up to the ganglion and

then centrifugal or antegrade spread (see Chapter 7) towards the other regions innervated by the other rami of the trigeminal nerve. This could also explain the subcutaneous metastases all over the face described in several cases (fig. 13.30)

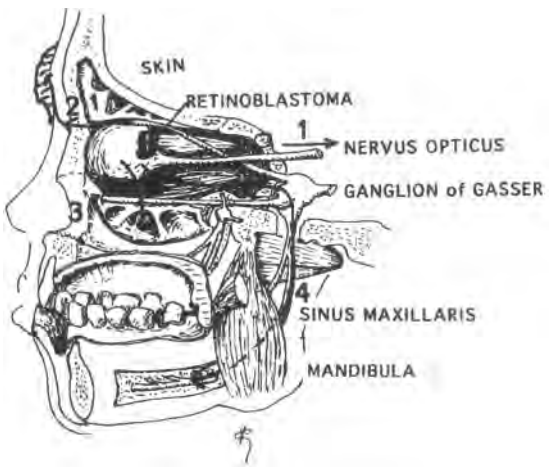

Fig.13.30 - The most frequent metastatic routes of spread of a retinoblastoma. 1. Along the optic nerve to the brain; 2. along the nervus trigeminus to the skin.; 3. invasion from the orbit to the maxillary sinus; 4. along nervus mandibularis to the mandible.

Table 13.97 -Retinoblastoma Metastases to the Oral Cavity

Author	Pat	Eye	Metast	Interv
Dunlap 1968	F2	Le	Le mandible	2 yrs
Pullon 1974	M9	Ri/Le	Le mandible	Simult
Pullon 1974	M2	Ri	Skull, maxilla Ri.mandible	2 yrs
Perriman 1978	F3	Ri/Le	Le.mandible	1 yr
Perriman 1978	M5	Ri	Le.humerus, Mandible, skull	2 yrs
Soni 1978	F6	Ri	Ri.parotid	1 yr
Ebata 1991	F4	Bil	Ri.Maxilla	3 yrs

Bone Metastases

Distant bone metastases are commonly mentioned in the series, but rarely well documented in the reports. One repartition has been outlined above in the autopsy series of Merriam.

The case of Perriman et al. had a metastasis in the humerus. A metastasis in the fibula was seen in the case reported by Blank et al. Other have been cited in the orthopedic literature. Previously, Reed et al. reported on 4 cases, one in the tibia, one in both femurs and later in other bones, and one in both humeri. Further evolution disclosed several other locations, but at autopsy many more were found. The fourth case also had several metastatic foci as well as the further discussed epidural and intradural spread with compression and necrosis of the spinal cord.

There have been discussions in the literature on the usefulness of routine staging bone scintigraphy and bone marrow aspiration, but most authors agree that it is not justified to apply it routinely, in view of the low incidence.

Rare Metastases

A 36-month-old boy has been reported, who after a mandibular, a pleural and femoral metastases, presented with a metastasis in the left testicle (Kimball et al.).

METASTASES from OCULAR MELANOMA

Ocular Melanomas are relatively rare. They can occur in the uvea (choroid) or at the conjunctiva.

Local growth can extent to the neighbouring structures in a way very similar to the above-discussed pathways of retinoblastoma (fig.13.31).

Fig.13.31 - Spread of intra-ocular melanoma to the conjunctiva, intraorbital content and cervical lymph nodes (Dithmar et al., with permission)

Optic nerve extension has been described in 8 patients with choroidal and in 2 with iridial melanoma (Spencer, 1975). Spread to the conjunctiva has been reported by Jakobiec et al. and by Dithmar et al.

Uveal melanomas can also spread towards the cervical lymph nodes. Reviewing 77 patients, Tojo et al. observed cervical nodes in 5 or 6.5% of the patients, all having also distant metastases.

Table 13.98 - Choroidal Ocular Melanoma Cases reported of Contalateral spread Literature review by Coupland et al.

Author	Pat	Presenting Symptom	Interv
Philips 1949	?59	Proptosis	10 yrs
Foster 1957	?56	Proptosis, papiledema	4 yrs
Sobol 1980	M48	Proptosis, visual probl	6 yrs
Troeber 1980	F39	Headache, photophobia	9 yrs
Shields 1988	F62	Proptosis, nodules	52 mo
Orcutt 1988	F69	Proptosis	4 yrs
Bowling 1994	M39	Proptosis, papiledema	17 yrs
Hutchison 1994	?32	Proptosis	6mo
Coupland 1996	M71	Proptosis, pain	40 yrs

A particularity is the occurrence of spread to the con-

tralateral orbit and its content. Reporting on a case occurring as late as 40 years after enucleation, Coupland et al. could retrieve 8 other cases (table 13.98). Proptosis and vision problems are the main presenting symptoms.

Choroidal Melanoma

Choroidal melanoma, with its particularly high propensity to produce liver metastases, is one of the most bizarre metastatic associations in oncology. A particular feature is the long interval after first treatment, up to 42 years(Shields et al.), and the huge volume the hepatic metastases can reach.

Reviewing 25 patients referred to a tertiary center, Einhorn et al. stated that choroidal melanoma occurred in 6% of all the melanoma patients. The median interval between enucleation and diagnosis of metastasis was 43 months (3.6 years) with a range of 6 to 204 months (17 years). Only 5 patients underwent autopsy. The different metastatic sites are shown in table 13.99.

Table 13.99 - Choroidal Melanoma
Distant Metastases - Clinical (N=25)
Data of Einhorn et al.

Clinical		Autopsy (N=5)	
Liver	22	Liver	5
Bone	3	Lungs	4
Subcutaneous	5	Heart	3
Stomach	1	Bones	3
Pleura	1	Diaphragm	1
Lungs	2	Pancreas	2
Axill.Node	1	Kidneys	1
		Stomach	1
		Thyroid	1
		Testis	1

Table 13. 100 - Choroidal Melanoma
Distant Metastases observed

	Lorigan N=110		Rajpal N=35		
	Init.	Subs.	Init.	Subs.	Aut.
Liver	85%	92%	45%	26%	73%
Lung	17	31	17	23	52
Bone	16	23	3	14	24
Skin-subcut.	13	17	8	25	12
Lymph nodes	10	14	8	5	36
Brain	4	4	3	3	24
Adrenal	2	3			
Stomach	2	2			
Spleen	2	2			

Init.: at first diagnosis, Subs.: during follow-up; Aut: at autopsy

Similar data were reported by Char on 41 patients.
Reviewing 181 patients treated for uveal melanoma, Lorigan et al. found metastases in 110 patients, with 3 at presentation. The metastatic sites observed after a mean follow-up of 11 months (1-74 months) are in table 13.100.

The limited autopsy data show the extremely likely possibility of involvement of any organ, as is common at autopsies of malignant melanomas (see Chapter 14).
Liver is the most common site of metastases,usually early or almost always the first presenting. Reporting on 3 cases, Libeskind et al. have stressed that hepatic metastases are always associated with a significant degree of hepatomegalia, without ascites or venous collaterals, though they are rather painful and are accompanied by a profound alteration of the status of the patient. Icterus is rarely seen, in less than 10%, unless the biliary tract itself is concerned.

An unusual form of metastases is that to the contralateral eye, with involvement of choroid, orbita and/or eyelid. Reporting on a case in 1996, Coupland et al. reviewed the literature and could retrieve 8 cases. The interval ranged from 6 months to 10 years, though in their own case it was 40 years. Most of the patients presented with other metastase, mainly in the liver, though metastases in the brain and bone were also reported. Incidence data are not available.

Nine years after radiotherapy for a choroidal melanoma a F84 presented with frequent syncope-episodes. Echocardiography demonstrated a left ventricular intracavitary pedunculated mass, confirmed at surgery as a metastatic melanoma. There were no pulmonary metastases (Rosario et al.).
A thyroidal metastasis was the first sign of an uveal melanoma in a F72, reported by Gherardi et al. Another case (M71) was published by Colombel et al. as having metastases in the stomach, occurring 18 years after surgery.
Zachariades et al. mention a patient (M53) enucleated one year before he presented with cystic lesion in the mandible, confirmed metastatic.
Reporting on 29 cases, Zimmerman et al. described the status of every patient with the sentence 'died of widespread metastases'.

Conjunctival Melanoma

Conjunctival melanoma is less frequent. Reviewing 68 cases referred to a tertiary center, DePotter et al. found that 14 had developed distant metastases. The first site was in the preauricular nodes (5 patients), brain in 4, the lungs in 3 and the liver and bone in a single case each. The average interval was 3.6 years (range 0.9-7.9 years). The only feature associated with the incidence of metastasis was the presence of a local recurrence, but not in the patients treated at their institute. Cervical and preauricular lymph nodes were observed in 7 patients, but metastases in the brain, lungs, liver and bone were also observed.
Travis et al. have reported on 5 cases of conjunctival melanoma metastatic to the parotid nodes, but two of these patients also had distant metastases to the liver, spleen, kidney, lung and bone.
Metastases within the conjunctiva towards the eyelid

by lymphatic extension have also been described (Jakobiec et al.). Local extension within the orbit has been reported (Polito et al.).
Metastases to the gallbladder as confirmed at laparotomy occurring 18 months after enucleation in a F64 were reported by Murphy et al.

Melanoma of the Iris

Only 3% of the uveal melanoma involve the iris. Distant metastases in iridial melanoma are less frequent than for choroidal or ciliary body melanoma. The incidence of metastases is very low.
Up to 1990, Brown et al. could retrieve only 37 cases reported of which only 7 had metastatic confirmation. Most were reported with widespread metastases, but liver and bones would appear the most frequent. Metastases to the breast, the spleen and abdominal cavity are cited in particular cases.
Only 5% of the 1,054 patients of Shields et al. developed metastases. Risk factors were increasing age, elevated intra-ocular pressure, posterior tumor margin at angle or iris root, extra-ocular extension and surgery before referral. The metastases were detected at a mean of 5 years after diagnosis of the primary (median 3.8years). The site of the metastases were not reported.
Previously, seven cases with metastases have been reported by Sunba et al. from a consecutive series of 196 patients. The site of the metastases was reported rather inaccurately, as 'widespread melanosis over the skin and elsewhere'.

Particular Case-reports

A number of particular metastatic sites have been reported in the literature. We have grouped them on table 13.101. The different sites involved ar not uncommon in metastatic cutaneous melanomas.

Table 13.101 - Ocular Melanomas
Particular Metastatic Sites reported

Author	Pat.	Prim.	Metastatic site	I nterv
Travis 1977(')	F50	Conj	Liver, spleen, kidney	16 mo
Colombel '84	M71	Chor	Stomach (large curv)	18 yrs
Yanai 1985	M46	Chor	Extradural	9 yrs
Gherardi '85	F72	Uveal	Thyroid	Reveal
Shields 1985	F70	Uveal	Liver	42 yrs
Murphy 1987	F64	Uvea	Gallbladder (intra)	18 mo
RusselJones'88	F71	Chor	Brain subfrontal	Aut.
Schweinfurth'93	M75	Conj.	Skull Base	30 mo
Marsh 1996	F31	Chor	Placenta, Bone	1 yr
Wieselthier '96	F59	Cil.B.	Face,scalp,Ax.node	3.5yrs
Midena 1999	M59	Chor	Brain (temp.occ.)	27 yrs
Ruiz 1999	F74	Chor	Heart Le.Ventr.	9 yrs
Rosario 2000	F84	Chor	Heart Le.Ventr.	9yrs

(')Their five cases reported as parotid metastases are probably nodal.; Aut.: autopsy

METASTASES from Cancer of the LACREMAL GLAND

Primary malignant neoplasms of the lacrimal system probably account for 1 to 2% of the patients referred to an ophthalmology clinics.
We have collated the few case reports in table 13.102. There is no obvious pattern, probably due to the low number of patients.

Table 13. 102 - Malignancies of the Lacrimal System
Distant Metastases reported

Author	Pat	Histol	Site	Interv
Worthy 1951	??	Cancer	Widespread	??
Waller 1973	M46(')	Mixed	T3	Reveal
Faraci 1974	M70	Adenoca	Pulmo	Simult
Jordan 1988	M68	AdenoCa	Nodes	3 wks
Nakamura '99	F55	Ad.Cystic	Skin	--

(') see text

In the case reported by Waller et al., it lasted 5 years before the primary was found. As can be expected it was long time diagnosed as adenocarcinoma metastatic to bone from an unknown primary, as he first had vertebral metastasis, later in the iliac bone and in the scapula.
In some small series, evolution with distant metastases is mentioned without further details.

METASTASES from Other OCULAR TUMORS

Conjunctival squamous carcinoma rarely metastasizes. Nevertheless, Tabbara et al. could report on 10 patients, without stating the total number treated. The metastases mainly occurred (8/10) in the pre-auricular (parotid) nodes and less frequently in the cervical or submental nodes. In one patient, pulmonary and bone metastases were observed.
In a review of 33 cases of their own, Bhattacharyya et al. observed only 1 patient that evolved to the parotid nodes. Reviewing the literature, they concluded to an incidence of 0 to 4%.
An important lesson is that cervical node from an unknown primary should take in account a lacrimal or conjunctival tumor as well.

METASTASES from CERVICAL PARAGANGLIOMA

Cervical paraganglioma, previously called glomus tumors or even chemodectomas, have undoubtedly the proneness to metastasize. Incidental data are rare, but several case reports and small series have indicated the possibility of metastases occurring in a wide range of sites.

The extra-adrenal paraganglion system can be divided into several anatomical groups(fig. 13.32).

1. The branchiomeric paraganglia.
   They arise in association with arterial vessels and cranial nerves of the head and neck region. They include the jugulotympanic, intercarotid (carotid body), subclavian, laryngeal, coronary, aortico-pulmonary and orbital (ciliary body) paraganglia.
2. The intravagal paraganglia are located within the perineurium of the vagus nerve, usually at the level of the jugular or ganglion nodosum.
3. Aortico-sympathetic paraganglia arise in association with the sympathetic nervous system, particularly at the bifurcation of the aorta (retroperitoneal). They may be found along the courses of the iliac and femoral vessels (femoral bodies in the canal of Hunter) and in the thorax.

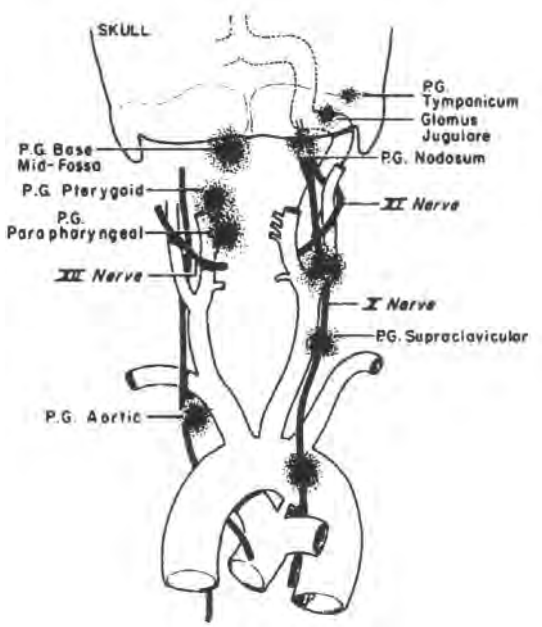

Fig.13.32 - Anatomy of the non-chromaffin paraganglia in the head and neck, the possible origins of tumoral paraganglioma. (Conley, with permission)

In the mediastinum, paraganglion tissue is also located along the costo-vertebral sulcus (near the sympathetic chain and in the anterior mediastinum.

Anatomical studies have confirmed the presence of the symmetrically located pairs of superior and inferior laryngeal paraganglia. The smaller, relatively constant superior group is related to the internal branch of the external laryngeal nerve (Watska) and are found in the upper anterior third of the ventricular fold near the superior edge of the thyroid cartilage.

When metastases occur (table 13.103), they are usually multiple with spread to the regional lymph nodes as well as to the lungs and bone. They can be defined as occuring in areas where no paraganglia are normally present, in order to differentiate them from the multicentric origin.
The clinical evolution of metastases is, however, very indolent. There are even reports of metastases that stabilized or regressed after resection of the primary (Bhansali).

Table 13.103 - Paraganglioma Incidence of Malignancy

Carotid Body	2-12%	Lymph nodes, lung, bone.
Vagal Body	10%	Lymph nodes, lung bone.
Jugulo-Tymp.	0.9-1.9%	Lymph nodes, lung, bone.
Larynx	<2%	Bone.
Aortic body	0%	
Retroperitoneal	28%	

(data of Ferlito, Barnes et al. and Olson et al.)

Some paraganglioma metastasize in the vertebrae, causing spinal cord compression. Brodkey et al. found 18 cases in the literature and added two. Remarkable is that there were 6 from a carotid primary, 3 other cervical and 4 not specified neck primaries, together with 1 mediastinal and 1 retroperitoneal paraganglioma. Five other primaries were not specified. Four years after a right neck dissection for a paraganglioma, a patient (F47) presented with neck pain, bilateral arm pain, numbness and diplopia. Imaging showed extensive lytic destruction and compression of C7 (Osborn et al.).

Carotid Paraganglioma

Reviewing the literature in 1977, Gaylis et al. estimated the incidence of metastasis anywhere to be 28%, with 20% in the lung and 15% in the bone.
Metastases from carotid paraganglioma were reviewed by Zbaren in 1985. They collected 106 cases of which 57 regional (nodal) and 49 distant metastases. The great majority were in the skeleton (22 cases) and in the lungs (17 cases). Metastases in the liver, the heart, the pancreas, the kidneys, the pleura, the epidural space, the thyroid and the skin were also described. Single cases of metastases in the diaphragm, the trachea, the brain and in the mediastinal nodes were also reported. The same authors estimate that the incidence of metastasesis probably about 11 to 12.5% if the total number of carotid body tumors reported are taken in account (table 13.104). It must be pointed out, however, that metastatic cases will be more prone to be published than the non-metastatic ones.

To our knowledge, only one case Has been reported where the patient presented first with numerous bone metastases of an unknown primary.
A 23 year-old man developed 5 years after surgery a pulsating mass in the right neck that turned out to be a carotid paraganglioma (Au et al.).
A review of the site of bone metastases shows that there is a slight majority in the cervical and upper thoracic vertebrae, compatible with some regional venous back-flow, probably along Batson's pathway.

Table 13.104 - Carotid Paraganglioma
Non-Regional Metastatic Site Reported
Review by Zbaren et al.

Bone	22 cases	Pancreas	3 cases
Lungs	17	Kidneys	3
Diaphragm	1	Skin	3
Heart	4	Epidural space	3
Pleura	3	Brain	1
Mediast.Nodes	2	Liver	4
Trachea	1	Thyroid	2
Epicanthus	1		

Jugulo-Tympanic Paraganglioma

Metastases from jugulotympanic paraganglioma are very rare. From a large series of glomus tumors, Alford and Guilford reported an incidence of 2%. Borsanyi estimated the rate to be about 4% in 200 literature cases. The most common areas of metastatic involvement are the lungs (35% of the metastases), the lymph nodes (47%), the liver (35%), bone (vertebrae, ribs) (18%) and the spleen. A recent literature survey by Manolidis et al. disclosed 25 cases. In their series, they had of 144 jugular tumors 9 or 6.3% cases. Bhansali et al. even reported hypercalcemia in one case with skeletal metastases.
The metastasis from jugular paraganglioma have extensively been reviewed recently by Brewis et al. They could retrieve 53 cases with 100 metastatic sites. The reported sites are shown in table 13.105 and do not appreciably differ from those reported for carotid paraganglioma.

Table 13.105 - Jugular Paraganglioma
Distant Metastases Reported
Review by Brewis et al.

Site			Other sites	
Lymph Nodes		19	Pancreas	2
Cervical	15		Pleura	2
Parotid	1		Back	1
Mediastinal	1		Bone marrow	1
Hilar	1		Bowel	1
Unspecified	1		Brain	1
Lungs		23	Chest wall	1
Bone		33	Epicardium	1
Skull	1		Nose cavity	1
Vertebrae	17		Nasopharynx	1
Ribs	7		Posterior neck	1
Pelvis	1		Retroperitoneal	1
Iliac bone	1		Spleen	1
Femur head	1		Spinal epidural	1
Femur neck	2			
Unspecified	3			
Liver		9		
Other		16		

An extensive jugulotympanic paraganglioma presenting with pain in the temporomandibular joint and trismus in a F33 was reported by Tashiro et al. At CT, a very large tissue mass was found to be invading the pterygoid muscles, the infratemporal fossa and the condyle of the mandible, the parotid gland and masseter muscles. At autopsy two months later, mediastinal, hilar and subcarinal lymph node metastases were found, but metastases also in the lungs, the left adrenal, several lumbar vertebrae and the sternum.

Compared with non-metastatic patients, there was a higher incidence of pain in the first complaints, probably due to the higher aggressiveness of the tumor, and a lower incidence of hearing loss, which is probably due to the fact that they manifest them at an earlier stage. There were no other statistical differences as far as demographic, clinical and other features are concerned.
If the mean interval between first treatment was 4 years and 6 months, it could be as long as 30 years.

Quite a number of cases of temporal paragangliomas have been reported as having 'spinal' metastases. Reporting on a case with a sacral metastasis, Gabriel et al. retrieved 6 cases from the literature, of which 4 at the cervical spine, indicating a regional (Batson ?) spread.

Vagal paraganglia give rise to a much higher incidence of metastatic dissemination, up to 19%. The sites are the same as mentioned above.
Some unusual cases have been published where cervical paragangliomas have metastasized towards the extradural space, causing spastic paraparesis. Parnell et al. reported on two cases, one originating from a vagal and one from a carotid paraganglioma.

SPINAL PARAGANGLIOMA

The central nervous system does not contain paraganglionic tissue. Nevertheless, intracranial and intraspinal paragangliomas have been reported.
The cauda equina seems to be the preferred location. Up to 1996, 80 cases have been published. There is a preponderance of females (M:F 1:2). The cauda equina tumors are benign in the sense that they do not metastasize Recently, however, Strommer et al. reported one patient with cerebellar metastases and Roche et al. a case with intra-cranial and intraspinal dissemination.
In an AFIP[1] series of 30 cases, 19 or 63% were in the lumbar region and only 8 (26%) in the region of cauda equina and filum terminale. No gender preponderance was noted and the median age was 46 years (20-74) (Moran et al.).
Most tumors will be intradural- extramedullar, and originate at the filum terminale and are encapsulated and hypervascular.

The clinical symptomatology is non-specific with low back or radicular pain with or without associated irradiation in the lower extremities. Paroxysmal hypertension has not been reported. MRI is the imaging method of choice. MIBG scintigraphy is useful for

[1]AFIP: Armed Forces Institute of Pathology, Washington

detection of metastases. After complete resection, recurrences are rare, but can occur even years after incomplete resection (Aggarwal).
CNS paragangliomas have been reported in the sella tursica, the pineal gland and the petrous ridge (Fitzgerald). A few paragangliomas of the thoracic cord have been reported. In contrast to cauda equina paragangliomas which are generally intradural, the spinal ones are almost always extradural.
The few reports on metastatic cord paraganglioma concerned intradural recurrence or spread, which is difficult consider as metastatic, unless there is seeding within the dural canal along CSF. One had invaded the vertebrae (Cybulski et al.), while others had metastasized extensively to the cauda equina (Blades et al., Constantini et al.).

Metastases from ESTHESIONEUROBLASTOMA

First described in 1924 by Berger et al., esthesioneuroblastoma (syn. olfactory neuroblastoma) is a rare neuroectodermal tumor originating from the olfactory (sensory, εστησιο-) epithelium. This epithelium extends from the roof of the nasal cavity to the midportion of the nasal septum and onto the superior turbinate with varying degrees of replacement by respiratory epithelium in the adult. At histology, these tumors present with neuroepithelial rosettes and undifferentiated cells with neurofibrils. The histology is similar to the infantile adrenal neuroblastoma and retinoblastoma, sometimes hardly to distinguish from sympathetic neuroblastoma.
The tumor occurs mainly in the middle and upper portion of the nasal cavity, occasionally in the lateral wall or the maxillary antrum. A literature review in 1980 by Bolla et al. disclosed that 77% of the 198 cases originated from the nasal fossa.
The tumor is characterized by its invasiveness and evolves alike ethmoidal tumors towards the cribriform plate into the intracranial content either leptomeningeal or/and intracerebral. Filling of the nasal cavity is common, while invasion of the orbit has been reported. Interesting data on extension were provided by Bolla et al. in a literature review on 196 cases (table 13.106). A case with infratemporal extension was mentioned by Schmidt et al.

Table 13. 106 - EsthesioNeuroblastoma
Loco Regional extension
Literature Data reviewed by Bolla et al. 1980

Site	N	Site	N
Ethmoid sinus	96	Palate	4
Maxillary Sinus	62	Cranial base(')	13
Frontal sinus	41	Nasopharynx	4
Sphenoid sinus	26	Oral cavity	2
Orbit	40	Mandible	1
Lam.Cribriformis	23	Cranial vault	1
Opposite nasal	4	Meninges	2
Brain	26	(') incl.sella tursica)	

Metastatic spread is not uncommon. Spread to the cervical nodes is well documented and may occur in up to 15% of the patients during follow-up (table 13.107). Some case reports mention submanibular and intra-parotid nodes. The rarity of these tumors limits adequate data on the spread, as most reports contain only a few cases, with inadequate follow-up length to deal with late recurrences of distant metastases.

Table 13. 107 - EsthesioNeuroblastoma
Data on Cervical Node metastasis from Literature

Author	N	Present	Follow up
Kadish 1976	17	-	4
Oberman 1976	7	-	1
Silva1982	29	-	5
Schmidt 1990	(4)	-	1
Beitler 1991	14	-	4
Davis 1992	(4)	3	1
Zappia 1993	21	-	3
Koka 1998	40	7	17
Levine 1999	35	1	1
	163	8(5.2%)	23(14.7%)

Table 13.108 - EsthesioNeuroblastoma
Data on Distant Metastases from Literature

Author	N	Distant Metastases
Fitz-Hugh 1965	6	1 with multiple bone and other
Tingwald 1966	7	Frontal lobe 1, hilar mass 1, frontal sinus 1
Castro 1969	7	Spinal cord (Th3-TH5) 1, 1 nodes everywhere + lung, liver, adrenal, vertebra
Kadish 1973	17	1 case
Oberman 1976	7	2 with lung metastases
Baker 1979	9	2 cases with spinal metastases
Feyerabend 1990	3	Th 7 osteolysis
Beitler 1991	14	Lung 1, bone 1
Eden 1994	40	FU 2 bones only, prostate 1
Slevin 1996	9	Lung 1, skin 1
Koka 1998	40	Simult.3, in FU in 16 Bone 11, skin 2, lungs 1, breast 1 meninges 3
Levine 1999	35	4 in Follow-Up

Table 13. 109 - EsthesioNeuroblastoma
Case Reports on Distant Metastases

Author	Patient	Site	Interva
Ranjan 1986	F56	Submandibular node	4 yrs
		intramedullary	4 yrs
		cerebellum	5 yrs
Carpentier '86	F75	Type 1 bilateral neck node	
		A: cauda equina	1 yr
Rodas 1986	M46	Frontal - parietal lobe	5 yrs
Massicotte '87	F58	Pulmonary nodule	10 mo
		A: choroid, lung,liver, adrenal, thyroid, heart, pericard, skin, pancreas, small bowel, mesentery, brain	
Link 1992	M51	Type 1 cervical node	--
Chatterjee '97	M56	Heart right ventricle	13 yrs
Shetty 2000	F13	Type 1 neck node	
		breast, axill.node, skin back, bone marrow, ovary	2 mo

Distant metastases are not uncommon. Reviewing the literature in 1990, Pape et al. could retrieve data on 240 cases, of whom 13.7% had neck node metastases and 10.8% distant metastases. The majority are in the lungs but bone is the second site. Metastases within the spinal cavity and/or medulla are quite frequent. Remarkable is that abdominal nodes have been reported in 5, while metastases have been reported also in the bone marrow, the heart, kidney, breast and mediastinum. Data retrieved from the reports are tabulated on table 13.108 and 13.109. Long intervals are not uncommon.

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Caution: References are given for documentary purposes. Not all have been reviewed or used in the redaction of the text. We do not claim completeness of data. The references are as much as possible grouped per subject heading. For some headings, only reports after 1974 are listed.

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14
METASTASES from TUMORS of the SKIN, SOFT-TISSUE and BONE

Epithelial tumors of the Skin
Adnexal tumors of the Skin
Malignant Melanoma of the Skin
Sarcomas of the Large Vessels
Osteogenic Sarcoma
Chondrosarcoma
Chordoma
Ewing's sarcoma
Soft tissue Sarcoma
Carcinoids
Extra-Pulmonary Small Cell Carcinomas

METASTASES from EPITHELIAL SKIN CANCER

Epithelial skin cancers present in two histologic forms, the basal cell or basalioma, and epidermoid cell carcinoma. Both have a somewhat similar local evolution, the basal cell being more destructive and resulting in the well-known ulcus rodens, a deep atonic destructive wound and tissue defects. Epidermoid cancers mostly result in a tumoral sessile mass, with much less invasion.
While basal cell carcinomas rarely metastasize along the lymphatics and nodes, this is more common in epidermoid cancers. The reason is most probably that the tumors remain out of reach of the blood vessels a long time and must grow to a certain volume or a certain invasion depth before cells can reach general circulation (Blewitt).
Another mode of spread is perineural spread, insidious and difficult to diagnose and prove, but very hindering and painful for the patient.

Distant hematogenous metastases, mainly to the lung and bone are uncommon, and usually the object of case reports and reviews.

Perineural Extension

As already discussed in Chapter 5, perineural extension is a misleading clinical situation presenting as pain within the territory innervated by a sensitive nerve involved by perineural tumor spread from a skin or deeper lying tumor.
It is an uncommon situation, but has been encountered in skin cancers, usually in patients who have had several necessary treatments, but also in some patients apparently cured after the first treatment. It is much more common in epidermoid than in basal cell skin carcinomas. In the series of MacCord et al., 46 had squamous cell cancer and 16 had basal cell histology.
Perineural extension can be the route to more distant CNS involvement such as in the cavernous sinus (Woodruff). et al.), and the meninges, even in the intradural subarachnoidal space (see also Bourne).
The patient (M35) reported by Pena et al. presented 15 months after treatment for a basal cell cancer at the right nasolabial fold, with typical symptoms of perineural spread and cytology finally confirmed leptomeningeal carcinomatosis
The incidence of perineural (symptomatic) spread is difficult to ascertain. Reviewing the charts of 520 patients treated for squamous cell cancer (at a tertiary center), Goepfert et al. documented perineural invasion at pathology in 72 or 14%. Symptomatology was clinically either absent or very variable (table 14.1).

Table 14.1 - Skin Cancer (Epidermoid)
Symptomatology in Perineural Invasion (N=72)
Data of Goepfert et al.

Asymptomatic	60%
Pain	28%
Anesthesia-Paresthesia	25%
Facial Paralysis	22%
Diplopia - Blurred Vision	17%
Decreased Corneal Reflex	4.2%
Jugular Foramen Syndrome	1.4
Trismus	1.4%

It was observed that regional lymph node metastases occurred significantly more frequently in these patients than in those without perineural spread. They also presented significantly more frequently with intracranial distant metastases (table 14.2).

Table 14. 2 - Skin Cancer (Epidermoid)
Associated pattern of Dissemination
Data of Goepfert et al.

	With PNI N=42	Without PNI N=448
Regional Lymph No	33%	15%
Distant Metastases	15%	3.3%
Brain	3/11	1/15
Bone	2/11	1/15
Lung and pleura	4/11	11/15
Other	2/11	2/15

PNI = Perineural Invasion

The authors observed proportionally more perineural invasion in cutaneous cancers at the midface (fig. 14.1), at the lip and around the mandibular division of the trigeminal nerve (table 14.3). We have added the data of MacCord in 62 patients for comparison, but the similarity is quite obvious. In the series of 21 cases reported by MacNab et al., 11 had a primary at the forehead or eyebrow with a further 5 at the midline.

Table 14. 3 - Skin Cancer (Epidermoid)
Cranial Nerves Involved in Perineural Spread

	Goepfert N=72	MacCord N=62
Cranial Nerve I	2.8%	11.3%
II	1.4	1.6
III	--	6.4
V1	9.7	11.3
V2	47.2	43..5
V3	12.5	17.7
VII	30.6	35.5
XI	1.4	--
Greater Auricular	1.4	--

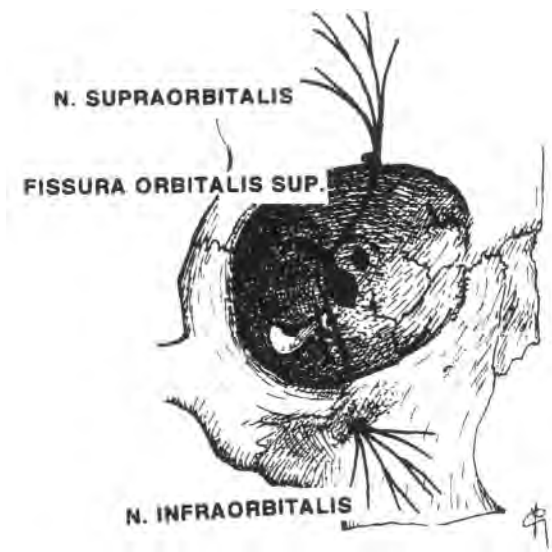

Fig.14.1 - Anatomic pathway of perineural spread from skin tumors of the forehead or of the cheek, along the divisions of the trigeminal nerve

Wgat is striking in this series is the absence of involvement of the oculomotor nerve, since it is much more frequently observed in the series reported later.
Alonso et al. have reported on two patients presenting after effective curative treatment of skin cancer at the frontal region, with ptosis of the upper eyelid and ophthalmoplegia (orbital apex syndrome, with n.III, IV and VI). At MRI, clear invasion of the sinus cavernosus was demonstrated.

MRI is certainly the most suitable imaging method to visualize the anatomy of perineural spread. Arcas et al. have outlined the features observed.

1. Concentric enlargement of the nerve;
2. Appearance of a tumor in the lateral wall of the sinus cavernosus;
3. Diffuse enhancement after i.v. administration of paramagnetic contrast medium;
4. Atrophy of the muscles innervated by the affected nerve.

Lymph Node Metastases

The propensity for epidermoid cancers to spread along the lymphatics and develop lymph node metastases is well known. Howevers, there have been several case reports of basal cell cancers presenting with lymph node metastases with or later in the evolution. The lymph node station where the metastases occur is obviously in the draining zone (fig. 14.2).

Not every cancer site on the face has the same incidence of lymph node metastases. Data are however scanty, but those of Lavedan et al. are very representative, showing that forehead and ear (pinna) have the highest incidence (table 14.4).
Lymph node metastases from basal cell carcinomas are rare. We found 19 case reports listed on table 14.5. some occurred after a long interval.

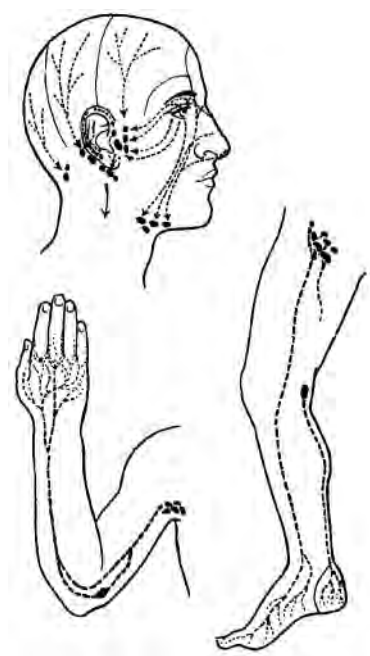

Fig.14.2 - Schematic view of the main drainage pathways from skin cancers (From Ackerman et DelRegato, with permission)

Various figures have been quoted for incidence of lymph node metastases in squamous cell cancer. A literature review by Dinehart et al. on 26 reports produced a range of 0.5% to 16.0%. The incidence will certainly vary according on the primary site, the size of the primary and on the number of recurrence.
The intra-parotid nodes are a particular lymphatic metastatic site. As described in Chapter 6 (fig.6.1), the peri- and intraparotid lymph nodes drain a large

part of the face, mainly the temple, the scalp and the peri-orbital region. The nose, lips and chin drain primarily to the submental and/or submandi-bular region.

Table 14. 4 - Cancer of the Skin Epidermoid
Incidence of Lymph Node Metastases according to site
Data of Lavedan et al. 1951

Site	N treated	N with node
Nose	136	13%
Palpebrae	55	22
Cheek	129	23
Temple	120	20
Ear (Pinna)	101	32
Forehead	62	2
Scalp	14	20
Chin	4	(1)

While several small series mainly addressing the results of the treatment have been reported, the largest series, regularly updated is that of the University of Florida (DelCharco et al.). They have accrued 77 patients who presented with a parotid swelling that turned out to be the first site of metastases after treatment of a facial cancer. The primary sites concerned are on table 14.6.

Table 14.5 - Basal Cell Skin Cancer
Lymph Node Metastases
Literature Review

Author	Pat.	Primary Site	Node	Interv.
Hughes 1973	M22	Le.cheek	Submaxill.	2 yrs
Hughes 1973	M47	Scrotum	Inguinal	2 yrs
Lildholdt 1975	M55	Ri.Retroauric	Neck	11 yrs
Lildholdt 1975	M53	Left leg	Inguinal	25 yrs
Weedon 1975	M37	Face-arm (mult.)	Axilla	35 yrs
Chandler 1982	M76	Upper chest	Axilla	7 mo
Domarus 1984	M44	Ri scalp	Neck	16 yrs
Domarus 1984	M54	Le.chin	Submand.	10 yrs
Domarus 1984	M27	Le cheek	Submand	3 yrs
Domarus 1984	M35	Ri.forehead	Pre-auric	11 yrs
Domarus 1984	F72	Le arm	Axilla	4 yrs
Conley 1985	F56	Ri.Eyebrow	Parotid	4 yrs
Conley 1985	F50	Ri.upper lip	Subment.	9 yrs
Conley 1985	M50	Ri.med.canthus	Parotid	8 yrs
Conley 1985	F69	Ri.lat. canthus	Submand	11 yrs
Davies 1995	M71	Ri.Up.eyelid	Pre-auric	10 yrs
Tavin 1995	M62	Le ear (pinna)	Parotid	6 yrs
Tavin 1995	M36	Nose	Submand	6 yrs
Tavin 1995	M80	Nose	Parotid	2 yrs
Tavin 1995	M74	Temple	Parotid	2 yrs

Table 14. 6 - Cancer of the Skin
Primary Site metastatic to Parotid Nodes
Data of DelCharco et al. 1998

Scalp	4	Upper lip	1
Forehead	13	Infra-orbital	5
Temple	14	Cheek	6
Eyebrow	3	Pre-Auricular	2
Canthus Int	1	Ear (pinna)	13
Eyelid	1	Ear lobule	3
Nose	3	Retroauricular	2

Differential diagnosis with a new primary in the parotid is mandatory. Furthermore not all reported cases can be considered as cases of ymph node metastases, as a number are clearly contiguous invasion from overlying skin cancers.

Distant Metastases

Hematogenous distant metastases in skin cancer are rare and the object of a number of reports.
The reported cases exhibit undoubtedly some regional association between the primary and the metastatic sites. This is especially remarkable for primaries at the chest metastasizing to the intrathoracal organs and/or bones.

Several authors have reviewed the literature on the subject. Conley could retrieve 19 cases of metastasized basal cell cancers in 1965, though in 15 it concerned regional lymph nodes. In 1977, an extensive review on 78 patients was reported by Mikhail et al., while Snow et al. had a similar but much shorter list.

Interesting epidemiological data, but dating back to 1968 on squamous cell cancer were reported from the California Tumor Registry by Epstein et al. (table 14.7).

Table 14. 7 - Cancer of the Skin - Epidermoid
Data from the California Tumor Registry 1968
Data of Epstein et al.

Patients with Skin Cancer (SC) Registered	6,900
Patients with true distant metastasis	142 = 2%
Regional Lymph Nodes	92
Distant Metastases	50
Bone Metastases	14
Lung Metastases	7
Other or generalized	21

Half of the patients with metastasis had their primary at the head, while the other half concerned patients with trunk or extremity cancers. This is not in accordance with the normal distribution; trunk and extremity primaries being about 10% of the incidence.

From a literature review in 1977, Mikhail et al. established the relative distribution of metastatic sites in the 78 reported patients (table 14.8).

Table 14. 8 - Cancer of the Skin- Basal Cell
Metastatic Sites in 78 patients

Site	Mikhail et al. 1977 N=78 pat.	Snow et al.1994 N=67(')
Nodes	49 : 41.1%	64.6%
Pulmonary	30 : 25.2	33.9
Bone	26 : 21.8	18.5
Liver	1 : --	--
Other	13 : 10.9	18.5
Total	119 sites	no data

(') 23 patients had multiple metastatic sites.

These data stress that about half of the metastatic sites are within the nodes and the other half true distant hematogenous metastases, at least in squamous cell cancers.

Table 14. 9 - Cancer of the Skin - Basal Cell
Primary Sites in 63 patients with distant Metastases
Review by Snow et al. 1994

Scalp	9.9%(')		
Temple	6.8	Non-facial	
Forehead	12.4	Neck	10.3%(")
Ear region	16.8	Trunk	52.0
Orbit region	11.8	Upper limb	9.1
Nose	8.1	Lower limb	9.1
Cheek	14.3	Other	19.5
Nasolabial	5.0	Total sites N=77	
Lip	5.0		
Chin	3.1		
Face	3.1		
Other	3.7		
Toatl N=161			

(') of the facial cases, (") of the non-facial cases

Reporting on 17 personal cases of metastasizing basal cell cancers, Farmer et al. cited only 4 with lymph nodes, but 9 had metastases in the lung, 5 in the bone and 3 in the liver. One also had metastases in the spleen and the adrenal, from a skin cancer on the chest.

Snow et al. reviewed the literature on metastatic basal cell carcinomas in 1994 and found 41 reports with 63 patients and 161 tumors. The most frequent region to metastasize would appear to be the region of the ear and the cheek (table 14.9).

Reporting on a personal series of 37 patients with distant metastases from squamous cell skin cancer, Tavin et al. noted that 9 were from the cheek and 7 from the temple, proportions somewhat different to those reported by Snow et al. for basal cell. Thirty nine of the 48 metastatic sites were nodal of which one-third to the parotid region and only 5 to the lungs.

Metastases to the Bone

Some reports do not make an appropriate distinction between invasion and true distant metastases. The titles of the reports can be very misleading, or contain too little information, and so the reportshave to be readcarefully.

Of the 20 cases retrieved, 5 were from a scalp lesion. From the reports, it can be deduced that most had different treatment for recurrent lesions and others had large neglected cancers with deep invasion. These are not true metastases.

Only 4 primary cancers were located at the trunk.

In a review of 585 patients with basal cell carcinoma, Amros et al. found only 1 case.

In some cases, the bone metastases were clearly regional, as cervical vertebrae associated with face lesions, and particularly the case of Albrecht et al. where a skin lesions at the lumbar region metastasized to the lumbar vertebrae and peri-aortal lymph nodes encasing both ureters at autopsy. In other cases as at the scalp with clear bony invasion and even destruction and associated with vertebral metastases, the pathway of Batson is a good explanation of the association.

Table 14.10 - Cancer of the Skin -Skeletal Metastases reported Literature Review

Author	Patient	Primary Site	Site of Metastasis	Interval
Basal Cell Carcinoma				
Stell 1966	M34	Le.Nasolabial	C2 -L1-L2-L3	6 yrs
Assor 1967	M60	Le.Nasolabial	Rib V - vertebrae middorsal	18 mo
Assor 1967	F53	Scalp (large)	Lower thoracic vertebrae	6 yrs
Assor 1967	M39	Back	Ri.Femur upper metaphyse	16 yrs
Cranmer 1970	M42	Back- Shoulder	Le.Femur (prox.epiphyse)	2 yrs
Cornelius 1970	M68	Face (multiple)	Pelvis - ribs - Spine	>10 yrs
Mantell 1972	M61	Shoulder	T7 - T9 -L3	14 mo
Mantell 1972	F60	Scalp (frontal)	Ankle - Foot - Humerus	26 yrs
Go 1973	M75	Upper lip	L2	2 yrs
Lildholdt 1975	F24	Ri.supraorbital	Humerus (proximal end)	7 yrs
Albrecht 1977	M62	Back (lumbar)	L2-L3	17 yrs
Christensen '78	M52	Left ear	L4	4 yrs
Schütte 1981	F45	Nasal tip	Ribs Vertebrae (autopsy)	>20 yrs
Rugge 1982	F46	Forehead	Multiple ribs	4 mo
Soffer 1985	F34	Ri. up. eyelid	C7 - Thoracic vertebrae	8 mo
Hartman 1986	M41	Le.temple	C2-C3+ epidural	20 yrs
Ambros 1988	M42	Ri..Nasolabial	C3 Clavicle Skull base	20 mo
Beer 1992	M43	Scalp (temp)	T7-T7-T8 - ribs femur	3 yrs
Oram 1994	M67	Scalp (oc-temp)	T4-T5-T6	6 mo
Wallny 1996	M61	Scalp (temp)	T12 to L4	11 yrs
BasoSquamous				
Lopes 1988	M58	Ear (pinna)	L2 + spinal cord compression	4 yrs.

According to Michel et al., the bone metastases from epidermoid cancer are usually single, while they are usually multiple in cases of basal cell cancer.
The case reported by Michel et al. is a clear contiguous invasion in the mandible from metastatic lymph nodes from a basal cell cancer of the nasal tip. In the case reported by Junor et al. a metastasis to the sternum is mentioned, but as the skin lesion was at diagnosis a large presternal mass, contiguous invasion is evident. This patient was also found at autopsy to have metastases to spleen and liver.

Table 14.11 - Basal Cell Skin Carcinoma
Bone Marrow Metastases
Cases Reported

Author	Pat.	Primary site	Interval
Coletta 1969	M68	Lower leg	1 yr
Beretta 1970	M55	Ri..lower eyelid	3 yrs
Jager 1977	M55	Ri..lower eyelid	17 yrs
Kleinberg 1982	F65	Skin upper back	Simult
Bason 1990	F51	Left Neck	Simult.

One particular type of bone metastasis readily encountered is diffuse metastatic skeletal metastases with nearly complete destruction of the bone marrow resulting in severe anemia; up to 5g Hgb. at presentation. We found five reports of this 'syndrome'. The diagnosis was confirmed by bone marrow biopsy in all patients (table 14.11).
Several cases have presented first with spinal cord compression. Weshler et al. have reported on a number of cases, but the reports were not available to us.

Pleuro-Pulmonary Metastases

Many case reports have been published of skin cancer patients with pulmonary metastases. We have listed them on table 14.12.

It will be seen that in the exception of one, all primaries were located at the head or the face. In nine patients there were multiple bilateral nodules, while in the others it consisted, at least in the beginning, of one relatively large mass. In two patients, pleural metastases with effusion was noted.
It is striking that in several patients, the basal cell cancer was a neglected one with deep invasion in the skull bone. Other patients had many recurrences repeatedly irradiated, excised or both.

One patient (F58) was treated several times for successive basal cancers on chronic radiodermitis of the scalp, after radiotherapy for a benign lesion of the scalp. She presented to the pneumologist with respiratory distress and on chest X-rays enlarged mediastinal nodes, which at mediastinoscopic biopsy were found to be of basal cell histology (Deygas et al.). A lymphatic pathway from the back to the paravertebral nodes has been described (Uren).
Another patient (M58) presented with dyspnea and was found to have pleural effusion without pulmonary nodules. At autopsy several pleural metastases invading the lungs were seen as well as mediastinal nodes. The primary, treated 7 years before, was located at the back (Degner et al.).
Fever, cough and hemoptysis were the presenting symptoms of a F59, three years after treatment for an ulcerated basal cell cancer at the axillary region. Chest X-rays showed a mass in the left lower lobe and at bronchoscopy, a polypoid mass or endobronchial metastasis was seen, with a biopsy typical of basal cell cancer (Papiris et al.).
The two latter patients are good examples of a segmental spread of skin cancer, with metastases to intra-thoracal sites.

Table 14.12 - Basal Cancer of the Skin - Pulmonary Metastases reported
Literature Review

Author	Patient	Primary Site	Site of Metastasis	Interval
Borghouts 1966	M66	Ri.Canthus intern.	Mass Ri..lower lobe	5 yrs
Baxter 1967	M43	Nose	Multiple nodules (autopsy)	>20 yrs
Lakshmipath '67	F75	Scalp frontal	Multiple nodules - pleural masses(Aut)	6 mo
Stewart 1968	M49	Face (zygoma)	Multiple nodules	>20 yrs
Wermuth 1970	M72	Ri.Nasolabial	Le.midlung, Le.upper lobe	3 yrs
Hughes 1973	M22	Le. Cheek	Pleural metastases + effusion	7 yrs
Sakula 1977	M52	Forehead	Multiple nodules - Pleural Effusion	16 yrs
Baker 1983	F58	Scalp (occipital)	Pulmonary nodules (3)	Simult.
Domarus 1984	M27	Le. Cheek	Multiple nodules	3 yrs
Domarus 1984	M35	Forehead	Multiple nodules	17 yrs
Conley 1985	M43	Upper Lip	Multiple nodules	20 yrs
Mikhail 1986	F44	Scalp	Multiple nodules	Simult.
Icli 1986	M33	Temple	Multiple nodules	3 yrs
Lopez 1988	F42	Forehead	Multiple nodules	16 mo
Beaulieu 1993	M17	Pretibial (leg)	Multiple nodules	9 yrs
Frizelle 1995	M61	Le forearm	Multiple nodules	6 yrs
Patel 1999	M66	Scalp (occipital)	Mass Ri. Lower lobe	5 yrs
Moll 1997	M74	Retroauricular	Ri. Upper lobe	16 yrs
Berti 1999	M53	Scalp (temporal)	Mass Ri. Middle lobe	13 yrs

Other Metastases

Hepatic metastases are rarely mentioned. A M80 presented with a neglected basalioma at the canthus internus. The tumor could be stabilized, but three years later histology-proven multiple hepatic deposits were detected (Postlethwaite et al.).
At autopsy of a woman with long-standing and repeatedly treated recurrent and new facial lesions, metastases in the spleen and myocardium were observed (Schütte et al.). Bourne mentions one of his four patients as having perineural invasion, a woman of 40 who developed paraplegia due to a subarachnoidal metastasis at L2-L3, seven months after diagnosis of perineural extension and 19 months after first treatment of a temporal skin cancer.

One particular type of metastases (or perhaps a regional continuous spread) is tumoral invasion within the oral cavity. The fourth case reported by Tavin et al. presented with invasion of the bottom of the nose, the palate and the alveoli extending from a skin cancer originally at the nose tip.
A painless intra-oral swelling over the mandible with deep invasion, bony destruction and invasion of the submandibular gland, confirmed at histology as basal cell cancer, occurred 5 years after treatment of a basal skin cancer of the upper lip (Silvester et al.).
The case reported by Blinder et al. is somewhat puzzling. A woman was treated for a large basal skin cancer at the right shoulder. Six years later, she presented with a fast growing mass at the mandibular gingiva, several months later within the right auditory canal. Biopsies disclosed a basal cell cancer in both sites.
Difficult to be considered as a distant metastasis is the patient reported by Demirkazik et al. with metastases in the breast. The patient (F38) had a squamous cell carcinoma on an extensive burn scar of the breast and upper abdomen. The tumors appearing in the breast several years after surgery were most probably a deep recurrence originating from deeply spread malignant cells.

METASTASES from ADNEXIAL TUMORS of the SKIN

Sebaceous carcinomas are rare. According to Warren, they comprise 0.7% of the skin tumors. Three quarters are on the face, 15% on the trunk and 10% on the limbs (Hernadez et al.).
A few cases have been reported as having nodal involvement (table 14.13) and less with distant metastases.
More patients have been reported with metastases from sweat gland carcinomas (table 14.14). Miller et al. in a literature survey found 34 cases (1967) of which 28 developed metastases, either nodes and/or distant. Later Jacobson found 32 cases of which 15 had distant metastases.

Table 14.13. - Sebaceous Gland Carcinoma
Cases with metastases

Author	Patient	Primary MM	Site of M
Beach 1942	M60	Ri.foot big toe	Ing.nodes
Warren 1943	M74	Skin temple	Reg.nodes
Constant 1968	F40	Pinna	Nodes
Hernandez '78	M72	Presternal skin	Axilla
Hernandez '78	M61	Presternal skin	Axilla

Sweat gland carcinomas are rare. They account for less than 1/1000 of malignant cutaneous neoplasms (Swanson et al.). They most commonly occur on the extremities and the head and neck, but also on the scalp, axilla and trunk of older people. According to the same author, 44 cases of metastatic sweat gland cancer treated with systemic chemotherapy have been reported.
A single painless firm nodular mass, often red or purple is the most common presentation. At histology, the most frequent type is the eccrine (poroma), a mixed group that usually arise from a benign poroma. The other histological type is the apocrine poroma, which is much less frequent.
The tumor derives from the epidermal acrosyringium, invades the upper dermis and dermal lymphatics, spreads in the lymphatics and will then reinvade the epiderm. Distant hematogenous metastases are not frequent. A frequent and usually first spread is cutaneous spread in the form of a myriad of nodules all over the affected region. This is the epidermotropism of skin metastases as has been described for some other primaries (Chapter 7).

Table 14.14 - Sweat Gland Carcinoma
Reports of cases with metastases

Author	Pat	Primary	Site of Metastasis
Damsgaard '69	F58	Epigastrium	Brain-skin-kidney
Meijer 1975	M63	Axilla skin	Axill.nodes
Briscoe 1978	M60	Ri.toe	Nodes Intraabdominal
Gögler 1978	F55	Ri.Index finger	Lungs (mult)
Shaw 1982	(2 of 27 cases: nodal metastases)		
Mehregan '83	M63	Foot plant	Hilar-Pulmonary
Morris 1986	M82	Heel	Nodes, Pleura
Swanson '87	M78	Le.shoulder	Nodes, intrathoracal
Borradori '88	M59	Ri.index finger	Plmonary nodules
Swanson 1989	M78	Le.Forearm	Pleural effusion
Dissana.1980	M46	Skin neck	Node-Spine
	F79	Sacral skin	Lungs
Roach 1983	M61	Ri.thigh	Node, Lung
Morrissey'88	M16	Plantar skin	Nodes, Bone
Kolde 1991	F75	(Multiple)	Abdominopelvic
Kolde1991	F82	Le.leg	Nodes pelvic
Dummer 1992	M74	Le.fingerV	Nodes
Bellman 1995	M68	Eyelid	SkinBone marrow
Barzi 1997	F64	Lumbar	Nodes, Retroperit
Grimme '99	M47	Scalp	Nodes, Liver-Kidney-Spine+
Ishikawa 2001	F37	Axilla	Widespread
Plunkett2001	F45	Scalp	Nodes, Lung, Rib

Table 14.15
Other Adnexal Skin Cancers with metastases

Agnoli 1971	F20	Rib-Clear cell (?)	Brain
Sandeson '75	F57	Scalp (AdenCyst)	Skin nodes

Two cases of skin cancers with an unusual histology and distant metastases have been reported (table 14.15).
Reporting on 14 cases of the very rare trichogerminoma, or tumors of the germinal hair epithelium, Sau et al. mention one patient who died of metastasis, though further details were not given.

METASTASES from SKIN MELANOMA

Malignant melanoma (MM) is a malignancy with the greatest aggressiveness and most widespread metastases of all. MM evolves from melanocyte precursors with the formation of intermediate lesions of varying stability.

Local Spread

MM will first evolve locally, penetrating the various different dermal layers towards the lymphatics and small vessels, but also radially within the skin (fig. 14.3).

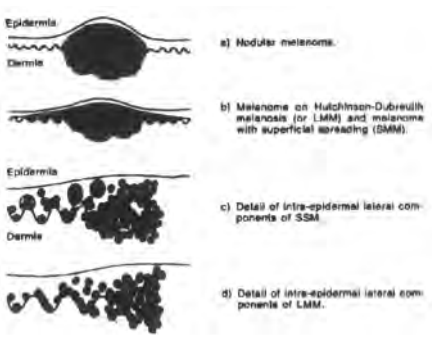

Fig.14.3 - Diagrams showing of the histology of a cutaneous malignant melanoma

Cutaneous involvement at some distance from the primary lesion is typical of MM. Various definitions are proposed in order to distinguish them from the common local recurrences and from the multiple primary MM (Cascinelli et al.).

Melanoma cells may spread by lymphatic permeation and can colonize the subcutaneous fat. Before reaching the regional nodes, these cells can be trapped within the lymphatics and give raise to satellite nodules.

Cutaneous Metastases

Local recurrence occurs as one or more nodule in the surgical scar. Satellite (cutaneous) metastases are in discontinuity with the primary and are arbitrarily set within a 5 cm radius of the primary, while those occurring further are called 'in transit' metastases. The distinction between both types of cutaneous metastases has, however, no prognostic value.
MM metastatic to the skin involves the subcutaneous fat or dermis, sparing the overlying epidermis, and is the overwhelming and most frequent type of cutaneous metastasis. In some rare cases, the metastatic cells will involve the more superficial layers and exhibit epidermotropism (reviewed by Heenan et al.). Another rare type of metastases is the zosteriform type, along a dermatome. Only three cases of MM should have been reported, according to Galindo et al.
A particular but rare type of skin metastasis simulating a blue nevus was stressed in a report by Busam. It occurred in the same anatomic region as the primary in the three patients reported and in the few retrieved from the literature. This is undoubtedly a potential pitfall.

Lymph Node Metastases

Lymphatic nodal metastases are well-known. MM drains to the regional basins in a similar way as skin cancer.
Data on the incidence of involved lymph node according to level (fig. 13.12) and to site of the primary have been provided by Shah et al. (table 14.16).

Table 14.16 - Malignant Melanoma
Lymph Node Metastases according to Site of Primary
N=111, Modified from Shah et al.

		Neck Nodal level, involvement in percent					
Site	N	I	II	III	IV	V	Par(')
Face	34	38.2	47.0	20.5	17.6	14.7	35.2
Scalp ant.	25	24.0	56.0	12.0	20.0	12.0	52.0
Neck ant.	16	12.5	50.0	31.2	18.7	25.0	6.2
Scalp post.	15	13.3	60.0	20.0	33.3	20.0	13.3
Ear	11	27.2	72.7	45.0	36.3	27.0	41.6
Neck post	10	0	50.0	40.0	10.0	30.0	0

(') Parotid nodes

Level I is quite frequently involved with a MM at the ear, the anterior scalp and neck. Overall, level II is the most frequently invaded, while level III will follows after level I. Parotid involvement is common in anterior scalp and ear lesion, but also frequent in face lesions, as one would expect on anatomical grounds. The frequency of involvement is, of course, much higher when the nodes are clinically enlarged.

Interesting data based on 132 patients who underwent a 'curative' inguinal dissecetion for MM were provided by Hughes et al. They give an insight on the relative frequency of primary site leading to inguinal metastases (table 14.17) (see also fig.7.36).
Primaries at the lower limb are the cause of an inguinal node in about 80%. Remarkable is that the median interval is shorter for foot lesions than for lower leg

and thigh lesions.

Table 14.17 - Malignant Melanoma
Inguinal Lymph Node Metastases and Site of Primary
Data of Hughes et al.

Site of Primary	N	Median Interval
Anter.Abdom. wall	6	4.5%
Back	4	3.0
Buttock	4	3.0
Foot	26	19.6
Lower leg	58	43.9
Thigh	20	15.1
Vulva	4	3.0
Unknown	10	7.5
Total	132	

Sentinel Lymph Node

Elective lymph node resection has been proposed in order to accurately stage the MM. It has however a significant morbidity not always obtaining the expected better survival. The sentinel node, the first node to which the tumor is drained can now be identified and resected due to an adequate technology development. This is particularly important in trunk melanomas as the sentinel node can be located at unexpected sites. Several authors have reported on their results and the method has become te accepted one as it yields adequate information. A negative sentinel node can make a further dissection superfluous.

Reporting on 348 sentinel procedures to stage regional lymph node basins in stage I MM, Wagner et al. made some important observations. A positivity rate of 19.6% was obtained, making further dissection unnecessary in 80% of the patients, with a significant lessening of morbidity and psychological benefit. There was a significant correlation with increasing tumor thickness and stage (table 14.18).

Table 14.18 -Malignant Melanoma
Sentinel Node Biopsy and Clinical Variables
Data of Wagner et al. on 348 procedures

Stage	Positive	Level	Positive
T1	2.8%	Clark 1	0
T2	10.8	Clark II	0
T3	26.1	Clark III	16.4
T4	42.4	Clark IV	22.9
		Clark V	25
Breslow <1.25mm	4.2		
Breslow >1.25mm	28.1		

The sentinel node technique is now well established for the management of MM. Important, however, is the knowledge that in a small group, sentinel nodes outside the regional lymph node basin can be detected in up to 10% of the patients, depending on the primary site. This has been examined by the group of Roozendaal et al. (table 14.19).
In-transit nodes, also called interval node metastases are defined as lymph nodes lying along the course of a lymphatic collecting vessel between a primary tumor and a draining node field (Uren et al.).

Table 14.19 - Malignant Melanoma
Sentinel Nodes outside regional Basin (N= 379)
Data of Roozendaal et al.

Primary Site	N	With aberrant Sentinel Node
Head and Neck	35	0
Trunk	133	11 (8.3%)
Upper Extrem.	58	4 (6.8%)
Lower extrem.	153	3 (1.9%)
All	379	18 (4.7%)(°)
Trunk	6 to the flank (4) and areola (2)	
	5 to triangular intermuscular space(')	
Upper Extrem.	2 to deltoid or bicipital sulcus	
	2 to epitroclear site	
Lower Extrem.	3 to popliteal fossa	

(°) excluding those not explored
(') lateral to scapula, surrounded by supra- infra-spinatus and long head of the triceps

The incidence of interval nodes presenting as sentinel nodes was examined by Uren et al. The difference between the different primary sites is striking (table 14.20).

Table 14.20 - Malignant Melanoma
In-transit nodes presenting as sentinel nodes
Data of Uren et al.

Primary Site	N	N with in transit sentinel
Posterior trunk	755	12.7%
Anterior trunk	150	7.3
Head and Neck	304	6.2
Upper limb	385	4.7
Lower limb	451	0.9
Total	2.045	7.2

Recurrence in Regional Nodal Basin

If the enormous literature on MM is replete with diagnosis, surgery and treatment of lymph node regions, precise data on the anatomic influence on recurrence are rare. The best data are from Calabro et al.

The most commonly cited features as gender, age, anatomical location, clinical nodal status and timing of dissection had no influence on the recurrence. Only the presence or absence of metastatic node and its number had a significant and independent correlation with the recurrence (table 14.21).

Table 14.21 - Malignant Melanoma
Failure in Regional Nodal Basin after dissection
(N=1001) data of Calabro et al.

Positive Nodes		Recurrence within basin	
Number of nodes :	1	9%	
	2-4	15%	
	5-10	17%	
	>10	33%	p<0.0005
Extranodal absent		15%	
metastases		28%	p<0.001

Table 14.22 - Malignant Melanoma
Incidence of In-Transit Metastases after dissection (N=1001) data of Calabro et al.

Risk Factor			
Site	Lower extremity	19%	
	Head and neck	5%	<0.0001
	Trunk	9%	<0.0001
	Upper extremity	8%	<0.01
Nodal basin	Inguinal	17%	
	Cervical	5%	<0.0001
	Axillary	9%	<0.005
Nodal failure	Inguinal	38%	
	Cervical	17%	<0.025
	Axillary	27%	NS

In-transit metastases occurred in 9.8% (Calabro et al.). The site of the primary, the location of the nodal basin, the clinical nodal status and any recurrence were the only significant factors (table 14.22). MM at the lower extremity had significantly more in-transit recurrences, the inguinal basin had the most either as location or when recurrence occurred within it.

In-transit recurrence occurred simultaneously with a nodal recurrence in 45 of the 142 (31.6%). It was 38% in the patients with an inguinal recurrence, while it was only 17% in cervical and 27% for axillary recurrence.

Distant metastases were observed in 677 patients (67.7%) in this group, but it was significantly lower in patients with a single node (60%) than when more than one was involved (80%, p<0.00001).

Distant Metastases

As with all malignancies with hematogenous metastases, the lungs are the most frequently involved, though the other organs also have a high rate of involvement, increasing in number towards death. Metastases have been detected in every part of the body.

Autopsy Studies - Distant Metastases

A thorough autopsy study of 216 patients who have died of melanoma has been reported by Patel et al. The lymph nodes are the most frequently involved, the lung parenchyme next. The overall incidence data are in table 14.23. The most common sites, observed in three-quarters of the patients are the lungs and the lymph nodes, though half of the patients have metastases in the liver, bone, brain, heart and GIT.

Compared with breast cancer, also a notoriously metastasizing tumor, melanoma has a higher incidence of metastases in the brain, heart and kidneys. Moreover, multiple organ involvement is common, less than 1% have only one metastasis in the series of Patel et al. (The authors have included an unknown number of ocular primaries) . A more detailed list is in table 14.24.

Similar data have been reported by Akslen et al.

Table 14. 23 - Malignant Melanoma
Distant Metastases- Autopsy data (N=216)
Data of Patel et al.

Lymph nodes	73.6%
Lung	71.3
Liver	58.3
Brain	54.6
Adrenals	46.8
GIT	43.5
Skin	10.6

Table 14. 24 - Malignant Melanoma
Detailed data on Metastases (N=216)
Data of Patel et al.

Respiratory	Lungs	71.3%
	Upper resp.tract	7.9
Gastrointestinal	Liver	58.3%
	Oral cav.-Esophagus	9.3
	Stomach	22.7
	Peritoneum	42.6
	Pancreas	37.5
	Small bowel	35.6
	Spleen	30.6
	Colon	28.2
	Biliary tract	8.8
Cardiovascular	Heart	47.2%
	Pericardium	24.1
	Major vessels	6.0
Endocrine	Adrenal	35.6%
	Thyroid	25.5
	Parathyroid -Pituitary	16.2
CNS	Brain	49.1%
	Meninges	24.1
	Medulla - pons	12.9
Urinary tract	Kidney left	34.7%
	Kidney right	31.9
	Lower urinary tract	13.0
Bone	Vertebrae	41.2%
	Other bones	33.3
Genital system	Ovaries or testes	
	Left	13.2%
	Right	10.2
Lymph nodes	Neck	42.0%
	Thorax	55.5
	Abdominal	56.0
	Pelvic	37.0
	Others	32.4
Soft tissue - Muscle - Skin		68.0

Gupta et al. reported on the metastatic disease observed in a large series of patients, treated for a stage HI or coming to autopsy, who developed extra-regional metastases. They found two groups of metastases, those occurring in more than 30% of the patients with metastases and those less than 30%. Some patients had solitary unusual metastatic sites although are apparently not uncommon in MM (table 14.25). The data show that MM can metastasize in every organs, even those rarely involved with other primaries.

Table 14.25 - Malignant Melanoma
Distant Metastases observed (N=652 (?))
Data of Gupta et al. 1964

Present in more than 30%			
Brain	39%	Liver	68%
Thyroid	39	Kidney	45
Lung	70	Adrenal	50
Heart	49	Pancreas	53
Spleen	36	Small bowel	58
Present in less than 30%			
Dura mater	5%	Mesentery	14%
Pituitary	5	Omentum	11
Breast	20	Peritoneum	13
Gallbladder	15	Colon descend.	22
Bile duct	6	Ovary	7
Cecum	5	Sigmoid	5
Stomach	26	Uterus	7
Pleura	24	Urin.Bladder	18
Pericardium	10	Testis	8
Diaphragm	17	Duodenum	12

The clinical pattern of the metastases is rather different. Some relevant data were published by Sacre et al. Stage has little or no influence, except for regional recurrences (table 14.26). However, the authors included local recurrences as first incident event, strongly maskin the data on distant metastases. The data are in table 14.27 according to gender. The parotid involvement probably relates to metastatic nodes from facial melanomas.

Table 14. 26 - Malignant Melanoma
Stage at diagnosis and first event (N=173)
Data of Sacre et al.

	Stage I	Stage II
Regional Lymph node	17.2%	51.1%
Local Recurrence	20.3	20.0
Skin	3.1	6.7
Brain	2.3	--
Bone	1.6	--
Parotid	--	4.4
Larynx	0	2.2
Lung	0.8	--
Liver	0.8	--

Table 14.27 - Malignant Melanoma
Pattern of Distant metastases and Gender (N=173)
Data of Sacré et al.

Site	Male N=75	Female N=98
Regional Node	37.3%	31.6%
Local Recurrence	33.3	29.6
Skin	20.0	4.1
Lung	8.0	6.1
Liver	2.7	6.1
Brain	8.0	1.0
Bone	2.7	4.1
Parotid	4.0	1.0
(Other less than2%)		

The timing or interval after first treatment has been addressed by O'Rourke et al. in 76 patients (table 14.28). As they have also done for several other cancers, DelaMonte et al. have analyzed autopsy data in 56 patients and subjected the data to cluster analysis. They conclude that malignant melanomas are a heterogenous neoplasm with cells of various metastatic potential. This constitutes, in fact, another definition of the 'seed and soil' features exhibited by most if not all cancers.

Reviewing the data of 62 MM-autopsies, Akslen et al. also observed certain patterns. CNS involvement was associated with an absence of local cutaneous or lymphogenous spread and of metastases in the lung, liver or bones. They found two predominant clusters, one visceral with a wide dissemination and one CNS-cluster with cerebral spread but few other metastases.

Table 14. 28 - Malignant Melanoma
Interval of metastases after first treatment (N=76)
Data of O'Rourke et al.

Simultaneous - at diagnosis	27.6%
Within 1 year	36.8%
Between 1 - 5 years	19.7%
Beyond 5 years	15.7%

For the melanoma, the involvement of organs and tissues exhibited the following frequencies, in descending order: neurotrophic 75%, reticulo-endothelial 45%, endocrine 35% and mesoderm 25%. They could identify in fact three predominant clusters: liver, CNS and gut seeding.

Detection

Although metastases can be readily detected by clinical examination or classic imaging methods such as chest X-rays, CT or MRI, depending on the site of the metastases, nuclear medicine has always tried to detect them at the subclinical stage.
Several radionuclides or labeled molecules have been developed and applied to MM.
FDG or F-18-Fluoro-2-deoxy-D-glucose with PET or Positron Emission Tomography is presently the most applied, and is an effective imaging modality (Steinert et al.).
Sestamibi-Tc^{99m}, applied with SPECT[1] has a high sensitivity and specificity (Perrot et al.), while **Thallium-^{201}** has also been applied with good results. The reader is referred to the pertinent literature on the subject.

Thoracic Metastases

Ultimately, nearly all patients with MM will have any thoracic involvement. All possible kinds of involvement, pulmonary parenchyme, pleural effusion and mediastinal nodes and other have been observed. Dedicated reports to this subject are, however, not frequent.

[1] SPECT: Single Photon Emission Computer Tomography

The data published by Webb et al. give a good idea of the frequency distribution, though before the CT era, on 63 patients (table 14.29).

Table 14.29 - Malignant Melanoma
Thoracic Involvement at Chest-X-ray (N=63)
Data of Webb et al. 1977

Pulmonary Metastases	57
Solitary nodule	14
Multiple nodules	41
Miliary spread	8
Lymphangitic spread	5
Enlargement of Nodes	28
Pleural effusion	10
Atelectasis/Bronchial obstruction	8
Lytic bone metastases	6
Cardiomegaly	4

The same authors discussed the hilar and mediastinal metastatic nodes observed on chest X-rays (table 14.30). About half had hilar nodes. We now know that CT will detect a larger number of pulmonary nodules.

Table 14.30 - Malignant Melanoma
Hilar or Mediastinal Lymph Node Metastases (N=28)
Data of Webb et al. 1979

Nodal Enlargement	28
Hilar (Unilateral)	10
Hilar (symmetric bilateral)	5
Middle Mediastinal - Paratracheal	5
Hilar and middle mediastinal	8
Pulmonary Nodules	25
Multiple bilateral	18
Ipsilateral	4
Ipsilateral -solitary	3
Lymphangitis carcinomatosa	5
Segmental or lobar atelectasis	5

However, radiologicaly does not have particular specific features pointing towards MM, so that differential diagnosis with other pulmonary pathologies is always necessary, although the diagnosis will be obvious in most cases. Cahan et al. have reported that in 29 MM patients submitted to pulmonary resection, a separate primary bronchial cancer was found in 5, while during further follow-up, they were detected in 3 other patients, more than 9 years after the first excision.

The CT appearance of lung metastases of MM is variable. Most lesions are small, though larger ones are regularly observed. Feeding vessels are frequently observed (Fishman et al.).

The site of the metastases within the lung is hardly ever reported. The data of Harpole et al. who reviewed 910 patients submitted to pulmonary resection, are undoubtedly from a biased group (table 14.31). Sixty percent of the patients amenable to surgery had bilateral involvement, and in more than 60%, multiple lobes were involved.

Table 14. 31 - Malignant Melanoma
Intrapulmonary Site of the Metastases (N=910)
Data of Harpole et al.

Right lung	23.4%	Upper Lobe	12.9%
Left lung	16.9%	Middle lobe	6.9%
Bilateral	59.6%	Lower lobe	14.9%
		Multiple	65.1%

Spontaneous pneumothorax has been reported in some patients (Yeung et al.).
We have not found any studies specifically addressing the pulmonary lymphangitis in MM.

Abdomino-Pelvic Metastases

Shirkhoda et al. have evaluated 202 patients with MM who had had an abdomino-pelvic CT. However, they do not state what prompted the CT, though it was probably routine staging, nor do they mention the stage of disease of the patients. They detected pelvi-abdominal metastases in 122 or 60%. Thirty-two patients had single-organ metastasis and 90 or 73% of those with metastases had multi-organ involvement (table 14.32). These data are very indicative, as f.i. they found a high number of metastases in the subcutaneous fat and mesentery. This data should have been correlated two darks' level or Stage. The number of metastases according to the site of the primary was well examined (table 14.33).

Table 14. 32 - Malignant Melanoma
Pelvi-Abdominal Metastases at Staging (N=202)
Data of Shirkhoda et al.

Lung base	49 (24.2%)	Abdomin.Nodes	75 (37.1%)
Liver	46	Mesentery	16
Spleen	9	Bones	14
Kidney	8	Subcutaneous Fat	17
Adrenal	28	Gallbladder	3

Table 14.33 - Malignant Melanoma
Pelvi-Abdominal Metastases and Site of the Primary
(N=202)Data of Shirkhoda et al.

	N	Abn. Nodes	Liver	Lung	Adrenal
Trunk	70	43 67%	50%	44%	21%
Upper Extr.	33	16 63	50	56	31
Lower Extr.	37	19 90	16	21	21
Head-Neck	29	23 48	26	44	30
Eye	9	7 14	86	29	--

The high number of patients with metastases in the H&N group (80%) is somewhat surprising, but again, the stage of disease was not mentioned.

Metastases to the Liver

Liver metastases are observed at autopsy in 30 to 60% of the patients. The liver is a common site for melanoma metastases. With CT, Shirkhoda et al. found liver metastases in 22,7%.
In a report concerning recurrences (nodal and distant)

during follow-up, Martini et al. state that liver metastases occurred in only 6%, but accounted for 34% of the distant metastases after treatment of stage I MM.
At CT, the hepatic lesions are variable in size, ranging between 0.5 to 15 cm. They are rarely single. The incidence correlates with darks' invasion level (Kamel et al.).

As CT is generally used for staging, the CT features are important for diagnosis. According to Chomyn et al., the great majority (no data) are not 'hypervascular'. In their technical study, they simply mention that 11 of the 19 patients studied had multiple liver lesions that were very suggestive of the diagnosis of metastases.
CT images obtained in 20 patients only during the portal venous phase would have resulted in 8 or 14% overlooked lesions, so that the study should be done in more than one phase. They were able to detect 57 liver lesions or 2.85 per patient.
Since the radiological images of liver metastases in MM are variable, CT examination should include all phases after contrast-injection.
It should be noted that MM metastases rarely invade vessels. Any vascular invasion should raise suspicion of other pathologies (Kamel et al.).
Reporting on MR imaging in MM on 41 patients, Premkumar et al. also observed a wide variation in the images of MM, but data on the pathology were not given.
In a report concerning recurrences (nodal and distant) during follow-up, Martini et al. state that liver metastases occurred in only 2.5%, but accounted for 14% of the distant metastases after treatment of stage I MM.

Metastases to the Biliary Tract

MM is the most frequent primary to metastasize in the gallbladder (table 14.34). About 15% of the patients will have gallbladder metastases at autopsy. The metastases are commonly at the mucosal surface and small.
A literature review by MacFadden et al. in 1979 could retrieve 10 cases.
When the mucosa of the bile ducts is involved, obstruction symptoms will develop and filling defects will be seen at imaging. Echography is very useful as first imaging method.
Symptomatology is commonly epigastric pain, but obstructive jaundice has been reported. The case of Langley et al. presented as a cholecystitis. Of the 14 cases they retrieved from the literature, 10 were in female patients. No particular primary site is observed.

Abdelli et al. noted that in 7 of the 23 reported cases a bile stone was detected within the gallbladder or duct.
Dong et al. were able to report on 19 cases from a single institution in 1999. Contrary to what was mentioned above, only 4 of the 19 were female patients. The primary site was at the skin of the trunk in 12 (63%). The mean disease interval was 40 months (range 2.4 mo-10 yrs). The patient described by MacArthur et al. had hemobilia due to an intraluminal metastasis in the common duct.

Table 14. 34 - Malignant Melanoma Metastases to the Bile Tract Some case reports

Author	Pat	Site of P.	Symptom	Interval
Gallbladder				
McFadden '79	F21	Cheek	Colics	3 yrs
McFadden '79	F50	Neck	Jaundice	9 yrs
Goldin 1990	F25	Ri.shoulder	Epig.Pain	3 yrs
Bugnon 1991	F32	Le.leg	Bile Colics	4 yrs
Gawenda '95	M52	Flanck	Abd.Pain	10 yrs
Abdelli 1996	M74	Cheek	Bile stone	2 yrs
Langley 1997	F40	Back	Epig.Pain	2 yrs
Common Bile Duct				
Daunt 1982	M68	Forearm	Jaundice	3 yrs
MacArthur '83	M31	Shoulder	Jaundice(°)	Reveal
OConnell '84	F52	Shoulder	Epig.Pain	18 mo
Kohler 1987	M61	Index finger	Jaundice	2 yrs
England 1990	M70	Back	Epig.Pain	3 yrs
Parquier 1991	F58	Le. leg	Jaundice	3 yrs
Thompson 1993	M42	Back-shoulder	Jaundice	5 yrs
Garas 2000	M31	Abd. wall	Pain, fever	3 yrs
Garas 2000	M57	(Face)	Jaundice	2 yrs

(°) jaundice and dark stools, with hemobilia

Metastases to the Spleen

MM is also the most frequent primary to metastasize in the spleen, although they are rare, fewer than 5%. The size of the metastases can be large and sporadically evolve to a spontaneneous rupture (Buzbee et al.). The patients will usually have multiple other metastases. With CT, Shirkhoda et al. found splenic metastases in 4.5% of the patients.
Abdominal pain in the left abdomen brought one patient to the hospital. At laparotomy, a giant (30x23x17cm) spleen was resected, containing multiple metastases. The patient (M69) had been treated for a MM at his back only one year ago (Kyzer et al.)

Metastases to the Kidney

Although mentioned in the autopsy report (25 to 35%), no clinical report is at hand, with the exception of discussion by Kamel et al. They stress the variability of the imaging features observed. Rarely is perirenal involvement observed, as well as calcification of the metastases.
Reporting on 71 patients with metastases in the urinary tract, Goldstein et al. mention 9 patients with renal metastases visible at urography, while at autopsy renal involvement was detected in 55 patients.

Lesions in the renal pelvis or ureter were easier to detect at urography because of the intraluminal defect.
The appearance at CT of renal metastases is variable. They can be single or multiple, small or large and

solid or cystic. Metastases in the posterior pararenal space have been reported and metastatic MM is the most frequent tumor at that site (Shirkhoda et al.).

Metastases in the CNS

While the incidence in the MM-patients is relatively low, MM is the third most frequent source of brain metastases in oncology. The incidence of metastases is much higher at autopsy than during clinical evolution, although large series have been reported.

The actual incidence from a tumor register have been reported by Cohn-Cedermark and by Sampson.
The first collected data were from the Swedish Cancer Registry from 2,456 consecutive cases of cutaneous melanoma over a period of 10 years, of which 189 (7.7%) developed brain metastases. It was the first event in 41 patients (1.6%) and 127 had distant metastases in other sites before the diagnosis of CNS metastases.
Other important epidemiology data are in table 14.35. CNS metastases are much more frequent in the male cohort, in MM at the trunk and at higher Clark's level of invasion or tumor thickness (data not shown). Bullard et al., reporting on 1,341 patients with 107 patients with CNS metastases, could not detect any difference in propensity according to the primary site of the MM. However, Sampson et al. found that primaries on the trunk and at the face had a significantly higher number of CNS-metastases, while those at the extremities apparently less(Table 14.36).

Table 14.35 - Malignant Melanoma
Epidemiologic Data of Swedish Cancer Registry
Data of Cohn-Cedermark et al. 1998

	Total	With CNS-Metastases
Male patients	1,249	125 or 10%
Female patients	1,396	64 or 4.5%
Distribution according to Primary Site		
Trunk	1,187	113 or 9.5%
Upper Extremity	355	13 or 3.6%
Lower Extremity	711	41 or 5.7%
Head and Neck	392	22 or 5.6%

Table 14.36 - Malignant Melanoma
CNS metastases
Comparative distribution of primary site
Data of Sampson et al.

	No CNS metast. N=6,251	With CNS metast. N=670
Trunk	37.6%	43.9%(')
Head and neck	15.8	18.2%(')
Lower Extremity	21.5	14.9
Upper Extremity	14.6	10.2
Eye	5.1	1.9
Mucosa	1.3	1.9
Other	0.0	0.0
Unknown	4.1	9.0

(') p<0.001

Symptomatology is no different from that described for other cerebral metastatic series, but leptomeningeal carcinomatosis would seem relatively rare. Only a few authors have reported on symptomatology, as usual in a very inhomogenous way, making comparison difficult (table 14.37). Overall, this will also depend on the anatomical distribution within the brain.

Table 14. 37 - Malignant Melanoma
CNS Metastases - Symptoms and Signs

	Choi 1985 N=194(')	Saha 1994 N=117(")	Gupta 1997 N=31(")
Sign			
Increase ICP	52.6%	---	35%(°)
Headache	---	15%	55%
Motor Symptoms	38.7	43%	26%
Cranial Nerves	26.3	---	---
Seizures	24.7	20%	32%
Mental Change	22.2	14%	26%
Dysphasia	---	---	6%
Abnormal Reflexes	17.5	---	---
Cerebellar Sympt.	13.9	---	---
Sensory Symptoms	10.8	---	---
No Symptoms	17.5	---	---
Other	---	8%	6%

(') radiotherapy series; (") unselected; (°) nausea

Table 14. 38 - Malignant Melanoma
CNS Metastases - Symptoms and Signs
Data of Mendez et al.

	Solitary Meta N=22	Multiple Meta N=33
Sign-Symptom		
Headache	36	26
Hemiparesis	24	21
Seizures	15	16
Visual Disturbance	5	1
Hempiplegia	2	1
Speech Disturbance	5	5
Confusion	5	16
Dizziness	5	1
Memory Loss	3	5
Abnormal Behavior	0	1
Others	0	7

Table 14. 39 - Malignant Melanoma
CNS Metastases - Anatomic Distribution

	Bullard 1981 N=86	Mendez 1988 N=55(')
Site		
Frontal	14.0%	9%
Temporal	5.8	5
Parietal	20.9	40
Occipital	8.1	9
Cerebellum	1.2	3
Multiple	37.2	---
Spinal cord	9.3	---
Meningitis	3.5	---
Both hemispheres	---	34

(') 33 patients or 66% had multiple sites

Mendez et al. have reported the symptomatology according to single or multiple involvement (table 14.38). Confusion tends to be present when multiple

lesions are present, but the symptomatology does not differ in patients with single or multiple lesions.
Only a few authors have reported on the anatomical distribution within the brain. We have selected some in table 14.39. The parietal lobe seems to harbour the highest number of metastases, which will correlate with seizures, motor or/and sensible symptoms.
In the series of Sampson et al., 39.2% had a single brain metastasis, 13.2% had two metastases, 7.8% had 3 metastases and the other 39.8% had more than 3 metastases.

Table 14.40 - Malignant Melanoma
Brain Metastases: Site of Primary and Size of Metastases
Data of Merimsky et al. (N=30)

			Size of Metastasis		
Site	N	NofM	>1cm	1-4cm	>4cm
Head Neck	6	17	5(1)	10(3)	2(2)
Trunk	8	21	5(1)	15(6)	1(1)
Upper limb	6	11	2(1)	6(5)	3(3)
Thigh-Leg	6	9	4(2)	5(3)	--
Foot	2	3	1(1)	2(1)	--
Eye	1	7	7(1)	---	--
Rectum	1	1	---	---	--

a(b): number of metastases(number of patients)

Hirst et al. have reported on two patients presenting during follow-up with a chiasmal syndrome, both due to a metastasis in the suprasellar region. In one patient the primary was a choroidal melanoma.
Reviewing 30 patients with CNS metastases from a MM., Merimsky et al. examined the correlation between site of the primary and the size of the metastasis (table 14.40) as well as between size of the metastasis and symptomatology (table 14.41). The latter has no specific significance, as symptomatology is more dictated by site within the brain. The authors did not address this relationship.

Table 14. 41 - Malignant Melanoma
Brain Metastases: Symptoms and Size of Metastases
Data of Merimsky et al. (N=30)

	Size of Metastasis		
Symptom-Sign	>1cm	1-4cm	>4cm
Asymptomatic	5	3	0
Altered Consciousness	1	0	1
Non Specific Complaints	3	8	5
Neurobehavioral Changes	3	5	2
Hemisyndrome	3	6	2
Visual Disturbance	0	2	0
Cerebellar Dysfunction	2	1	3
Cranial nerve Palsy	0	3	0
Seizures	0	2	0
Papilledema	0	1	0

Imaging features at CT and MRI have been discussed by several authors. At CT, the unenhanced metastases appear as hyperdense lesions in 85% of the patients. They are usually located at the grey-white matter junction, as most metastases are. At MRI, they show typical Tl and T2 shortening. The occurrence of intra-lesional hemorrhage leads to a paramagnetic effect. Melanin must be considered the cause of the T1 and T2-shortening (DeWulf et al.).
Reviewing the cranial CT of 312 patients with confirmed MM, McGann et al. have reported their findings. Intracranial disease occurred in 89 patients (table 14.42).

Table 14. 42 - Malignant Melanoma
CT-features of Intracranial Metastases (N=89)
Data of McGann et al.

Multiple lesions	64%	Hemispheric	not given
Size 2cm or less	53	Cerebellar	not given
>2cm	23	Particular sites	
both	13	Diffuse meningeal	5
Attenuation (non-enhanc.)		Tentorial edge	2
High	76	Orbits	2
Low	1	Corpus callosum	5
Isodense	5	Superior vermis	2
Mixed	7	Skull vault	3
Contour nodular	80	Third ventricle	1
irregular	9	Midbrain cistern	1
		Cerebellopont.angle	1

According to Holtas et al., all cerebral metastases of MM have a higher density than surrounding tissue after contrast enhancement. Typical MM metastases are round, homogenous and with a regular border. The surrounding edema increases in frequency with size. They also note a correlation between size of the lesion and the presence or absence of neurological symptoms, which one would think is quite obvious.

Ophthalmic Metastases

Ophthalmic metastases are relatively infrequent in malignant melanoma. However, compared with the other primaries, the metastases have another pattern, a multi-site involvement being more frequent.
Reviewing the literature in 1967, Font et al. retrieved 18 reported cases. If 15 were uveal, there were 6 at the retina, 4 in the vitreous, 3 at the iris and 2 at the palpebral conjunctiva. Nine patients had multi-site involvement. The authors reported on 10 additional cases, of which 6 were at the orbit, 4 in the choroid, 1 at the retina, 2 at the iris and 1 at the anterior chamber and conjunctiva. In five patients, more than one site was involved.
Reporting on 10 patients, DeBustros et al. also mention 6 patients with choroidal involvement, and 1 in the retina and 3 at the iris, of which 1 had also ciliary body involvement.

A non-exhaustive list of case reports is in table 14.43. The wide variation in metastatic sites is immediately obvious.

Melanoma metastatic to the orbit has also been reported several times and quite a number will have involvement of the ocular muscles. Orcutt et al. have reported on six cases of which one was an uveal primary. Symptomatology and signs are as discussed in

Chapter 6, and consist mainly of diplopia, pain, proptosis or inflammatory signs.

Table 14. 43 - Malignant Melanoma
Case Reports on Ophthalmic Metastases

Author	Pat	Primary	Site of M	Interval
Hirst 1979	F26	Shoulder	Le.iris	10 yrs
Char 1980	M72	Le arm	Vitreous	7 yrs
Char 1980	F27	Shoulder	Le.iris	??
Robertson '81	F43	??	Vitreous	3 yrs
Robertson '81	F37	Axilla	Vitr.-Retina	5 yrs
Letson 1982	M44	Axilla	Bilat.Retina	3 yrs
Cole 1986	M38	Shoulder	Vitreous	3 yrs
Oosterhuis '87	M38	Back	Ret+Iris-Vitr	3 yrs
Oosterhuis '87	M33	Leg	Lat.Rectus	1 yr
Pollock 1991	M36	Neck	Opt.Disc Vitr	10 yrs
Bacin 1992	F27	Back	Ri.Iris	31 mo
Bowman 1994	M63	Back	Iris, Vitreous lens capsule	6 yrs
Bell 1995	F26	Knee	Choroid	8 yrs
Spraul 1996	M55	Elbow	Retina-Vitr	2 yrs
Spraul 1996	F67	Arm	Retina-Vitr	3 yrs
Kwapiszeski '97	M52	Neck	Conjunctiva	3.5 yrs
DharMunch '00	M42	Back	Chor+Conj	2 yrs

Fishman et al. have reported on autopsy data. From a series of 25 patients who had died from widespread MM, they found involvement of the eye in 5 patients. Choroidal metastases were seen in 3 and retinal metastases in the two others.

Extraocular muscle invasion appears to be a favored site in metastatic melanoma. Orcutt et al. found that 3 of their 5 patients had developed this metastases, and found 21 cases from the literature with orbital metastases, of which 16 had muscular metastases (table 14.44).

Any ocular metastasis can either be the first metastatic recurrence of the melanoma, but most frequently is accompanied or preceded by the occurrence of other metastases.

Table 14. 44 - Malignant Melanoma
Ocular Muscles involved in Orbital metastases
Literature Review by Orcutt et al.

Rectus inferior	5
Rectus lateralis	5
Rectus medialis	2
Rectus superior	1
Multiple muscles	1

Head and Neck Metastases

Head and Neck structures are a favorite site for metastasizing malignant melanoma. Several case reports have been published (table 14.45). The majority concern metastases to the tonsil. A review of the literature, including two other series reported, shows that the majority of the MM metastases are within the tongue (table 14.46).

Four cases of involvement of the parotid gland have been reported, but they were most probably intragland lymph node metastases. Reviewing the literature on mandibular MM metastases, Santamaria et al. could retrieve 9 cases from 1941 on, and added one case.

Table 14. 45 - Malignant Melanoma
Head and Neck Metastases
Case Reports

Author	Pat	Primary	Site of M.	Interv.
Mosby 1973	M29	Axilla	Pharynx-Gingiva	15mo
Pliskin 1976	F23	Unknown	Gingiva	---
Meyer 1979	F21	Lumbar	Maxill.Antrum	15 mo
Craig 1982	M56	Calf	Tonsil	7y rs
Myer 1983	M49	Chest	Tonsil	5 yrs
Ferlito 1984	F75	Cheek	Epiglottis	32 mo
Ferlito 1984	M60	Ri.leg	Epiglottis	10 mo
Welch 1985	M23	'Mult'	Odontal cyst	2 yrs
Morgan 1985	M42	Chest	Supraglottis	3 yrs
Morgan 1985	M43	Chest	Subglottic	13 yrs
Bizon 1986	F41	Back	Ethmoid sinus	3 yrs
Rintala 1987	F51	Gluteal	Palate	4 yrs
Nicolaides'89	M55	Chest	Tonsil	18 mo
Vaillant '90	F55	Neck	Mandible	4 yrs
Sheppard '90	M48	Finger	Thyroid	2 mo
Ikeda 1991	M42	Le.leg	Epiglottis	32 mo
Cauchois '93	M41	Thigh	Tonsil	5 yrs
Stern 1993	F56	Forearm	Tongue(lat)	10 yrs
Stern 1993	M52	Forearm	Tongue(dorsum)	3 yrs
Ramamurthy'95	M32	Shoulder	Tonsil-Nasoph	2yrs
Aydogan 1996	M52	Palate	Tonsil	17 mo
Aydogan 1996	M31	Shoulder	Tonsil	2 yrs
SantaMaria '97	M55	???	Mandible	---
Cervio 1999	M39	Back	Int.Aud.Canal	10 yrs
Sood 1999	F73	Elbow	Tonsil	6 mo

Table 14. 46 - Malignant Melanoma
Sites of Head and Neck Metastases
Literature reports (*)

Tongue	31 cases	Lip	9 cases
Tonsil	26	Larynx	13
Palate	4	Nasopharynx	10
Gingiva	8	Pharynx	6
Mandible	14	Sinus Piriform	3
Maxilla	4	Buccal Mucosa	4
Nasal Cavity	3	Int.Aud.Canal	1

(*) Welch et al. literature review 1985; Henderson et al. series of 54 cases; Patton et al. series of 15 cases; cases of table 14.42

Cardiac Metastases

MM frequently involves the heart. Such metastases account for nearly 50% of the patients at autopsy. Nevertheless, the literature only has small series and case reports.

Several years ago, Glancy et al. published a landmark article on 70 autopsy cases, of which 45 or 64% had any cardiac metastasis. Their data on the involvement of the heart are very extensive (table 14.47).

The tumor had extended through the entire wall of one or more cardiac chambers in at least 15 patients, or one third. The symptoms and signs registered do not differ from the usual symptoms in cardiac metastases

and include dyspnea, peripheral edema and various rhythm disturbances. Any cardiac symptomatology presenting in a patient previously treated for MM should prompt for an echocardiography.

Table14. 47 - Malignant Melanoma
Pathology of Cardiac Involvement (N=45)
Data of Glancy et al.

Endocardium mural	73%	Atrial septum	49%
Tricuspid valve	4	Right ventricle	67
Myocardium	98	Left ventricle	73
Right atrium	76	Ventricular Septum	58
Left atrium	51	Epicardium	78

Several cases of cardiac involvement have been reported with some unusual, but pertinent symptoms (table 14.48). As usual, several patients had also other metastatic sites, as in the mediastinum. Details are not always reported.

Table 14. 48 - Malignant Melanoma
Cardiac involvement - Case reports

Author	Pat	Primary	Site of M	Interval
Thomas 1977	M30	Chest	Ri.A+V	6 mo
Waller 1980	F38	Thigh	Ri+Le R-A	2 yrs
Hanley 1983	F56	Nose	Le.Ventricle	22 yrs
Kutalek 1985	F59	Thigh	Ri+Le R-A	3 yrs
Emmott 1987	M60	Nose	Ri.Ventricle	4 yrs
Gindea 1987	M62	Nose	Ri.Ventricle	1 yr
Krishnan '89	F46	Leg	Ri.Atrium	2 yrs
Mindel 1989	F65	Back	Ri.Ventricle	27 yrs
Canver 1990	M32	Neck	Le.Atrium	5 yrs
Bortolotti '90	M49	Mult.	Pericard	Reveal
Sheldon '91	F35	Back	Le.Ventricle	10 yrs
Vetto 1992	M51	Chest	Ri.atrium	3 yrs
Schneider (94	M58	Thigh	Ri+Le R-A	7 yrs
Katz 1996	M59	???	Epicard	??
Legoux 1996	M50	Leg(?)	Pericard	3 yrs
Chen 1996	F56	Axilla	RA intracav.	26 yrs
Carpenter '97	F53	Elbow	Ri.V.(two)	17 mo
Petropoulakis'98	M58	Upper arm	Ri.A+V	10 yrs
Prabhakar'98	M65	Scalp	Ri.Atrium(')	7 yrs
Mousseaux '98	M46	Elbow	Le A+V	4 yrs
	M67	Thigh	Le V	Simult
	F63	Back	Le A	8 mo
	M50	Neck	Ri A	8 yrs
Burn 1999	F33	Forearm	Ri.Atrium	8 yrs
Gibbs 1999	F46	Neck	Ri.Atrium	25 yrs
Gibbs 1999	F74	Leg	Ri.Ventricle	23 yrs
Bossert 1999	F56	unknown	Ri.Atrium	Reveal
Savoia 2000	F45	Leg	no data	26 mo
	F39	Leg	no data	18 mo
	M50	Leg	no data	12 mo
	M60	Foot	no data	24 mo
	F53	Back	Ri.A+V	14 mo

(') patient with cerebral metastasis and patent foramen ovale

Reviewing several cases of cardiac metastases from MM, Hanley et al. suggested that cardiac metastases should be suspected in the occurrence of acute pericarditis, pericardial effusion or rapid enlargement of the cardiac shadow, any tamponade, an 'ectopic' tachycardia, an atrial tachycardia, a second or third degree AV-block or any congestive heart failure. However, the same signs occur in cardiac metastases from other primaries (chapter 1) and are not specific to MM.
From a series of 2,810 patients treated for MM, Savoia et al. could retrieve 5 cases metastatic to the heart, of which 4 were diagnosed clinically. Remark that of the 32 cases reported, 15 or almost half originated at the extremities.

Metastases to the Gastro-Intestinal Tract

Any patient who has been treated for a skin melanoma and presenting with GIT symptoms should be suspected of having metastases along the tract. They can occur several years, even more than ten, after first treatment.
Malignant melanoma is one of the most frequent primaries to metastasize to the GIT. Up to 5% of the patients will develop these metastases, of whom previously a large part, about 60% were found only at autopsy. Better awareness and more adequate diagnostic possibilities, such as endoscopy, will allow more frequent 'ante-mortem' diagnosis.
Of 6,509 patients treated for MM., 1,600 were at stage IV or with metastases (Ollila et al.). Of these, 124 or 7.7% had a GI-tract metastasis. Only 69 could be treated surgically. The anatomic sites were the small intestine (36%) followed by the colon (9%), the stomach in 6% and the rectum in 2%. A common combination was small bowel and colon, occurring in 14 patients or 17%.
The esophagus is an uncommon site. Symptomatology is obvious but aspecific, and include dysphagia, discomfort, weight loss or hematemesis/melena. The endoscopic aspect with multiple pigmented nodules, bulky, polypoid or intraluminal mass allow differentiation from the less frequent primary melanoma of the esophagus. One of the cases reported by Silverman was at the esophagus.
Gastric metastases should occur in about 30% of the MM patients. At endoscopy, two types seem to be preponderant, the ulcerated nodules or a mass lesion with necrosis and melanosis, though Taal et al. have also noted other patterns (table 14.49) At radiology, the typical 'bull's eye' image will appear.

Table 14.49 - Malignant Melanoma
Endoscopy pattern in upper GIT tract (N=22)
Data of Taal et al.

Pattern seen at	Esophagus	Stomach	Duodenum
Multiple nodules	1	5	5
Bull's eye	--	5	2
Extrinsic tumor	--	3	--
Ulcer	--	2	--
Polypoid mass	--	2	2

The lesions are more common in the distal jejunum or ileum than in the proximal small bowel. The melanoma cells deposit in the submucosal layer will result in an intraluminal mass, while cellular deposits in the serosa will result in compressing lesions and in

the mesentery will grow to large masses. Necrosis and ulceration is common in masses that grow further than their blood supply permits. Lymphatic spread from these secondaries is common.

More than half of the MM metastases to the GIT are located in the small bowel. The symptomatology is as variable as the small bowel pathology can be: bleeding, appendicitis syndrome, symptoms, weight loss, obstruction, malabsorption and protein-losing enteropathy. Perforation is remarkably absent or rare. Intraluminal polypoid lesion can lead to intussusception.

Conventional radiology will demonstrate mural nodules, 'target' lesions, large excavating masses or diffuse involvement. Enteroclysis is the study of choice, while CT will better delineate any mesenteric or omental involvement. The CT appearance of metastatic melanoma is difficult to distinguish from other tumoral bowel pathology. Infiltrating lesions, masses with or without ulceration can be observed.

Occasionally, the metastases can perforate and lead to an acute abdomen or peritoneal seeding with carcinomatosis (Fishman et al.). Patients with multiple lesions can remain asymptomatic. Intussusception has been observed.

An unusual case was reported by Kadri et al. A F72 presented with progressive anemia. GIT barium study disclosed stenotic images at the jejunum and ileum, and at laparotomy, eight distinct melanotic tumors had to be resected. Primary melanoma wa,s however, not present in the anamnesis and was not found, nor at dermatology or ophthalmology.

A large metastatic mass perforated, resulting in hemoperitoneum in a patient (M41) reported by Wong et al. This happened three years after first treatment for a MM at the calf. Stressing the variable pathology of the intestinal involvement in 6 case reports, Wilson et al. mention one patient (M58) presenting with melena, in whom 36 (!) polypoidal lesions were found in the jejunum.

The colon is the least frequent site of the tract involved by MM. Solitary lesions, particularly at the cecum, colonic intussusception, polypoid lesions, large ulcerative masses or submucosal nodules are visible at endoscopy or at pathology.

A solitary metastasis in the ascending colon (F66) was reported by Silverman et al., 20 years after excision of an axillary MM. Five years after treatment for a MM at the leg, a patient (F50) presented with bilateral inguinal nodes, multiple coin lesions on chest X-rays and at colonoscopy a subpedunculated lesion covered by normal epithelium in the descending colon. Histology confirmed their metastatic nature (Tamura et al.). The radiological images are very much like those in the small bowel.

Anal melanomas are more frequent primaries than metastatic lesions, and require adequate pathology studies.

Mesenteric or omental metastases will present at radiology as a serosal implant with indentation of the bowel lumen or masses without impinging on the lumen.

Mesenteric masses can grow to very large volumes, diameters of 25 cm having been reported (MacDermott et al.). Peritoneal carcinomatosis or omental cakes are not uncommon. Several surgical series have been reported. A well-documented series of Caputy et al. on 41 patients is in table 14.50.

Table 14.50 - Malignant Melanoma
Gastro-intestinal Metastases -Surgical series (N=41)
Data of Caputy et al.

Symptoms		Signs	
Fatigue	63%	Hemorrhage appar.	37%
Pain	56	occult	20
Anorexia	46	with hypotension	10
Obstruction	44	Abdominal mass	34%
Dysphagia	2	felt by patient	20
		Weight loss >5kg	22%
Site of metastases			
Esophagus	5%	Small bowel	71%
Stomach	27	Large bowel	22%

Of 230 patients treated for MM, 17 developed gastrointestinal metastases, or 7.4%. (Kawashima et al.). At routine staging, Shirkhoda et al. found metastases to the bowel or mesentery in 8%.

Bone Metastases

Metastases from MM to the skeleton are not common, but almost all sites within the skeleton can be involved. There is a significant discrepancy between autopsy data which show an incidence of 30 to 45%, while clinical series suggest 5 to 10%. (Stewart et al. 1978: 6.9%; Spiegel et al. 1995: 5%).

Clinical series have probably tended to report more on symptomatic metastases, while it has been shown that many are asymptomatic. Reporting on 50 patients with 127 metastases, Fon et al. observed that the axial skeleton was involved in 80% and the ribs in 38%. In 29 patients with solitary metastases, 11 or 38% had rib metastases (Fig. 14.4).

Spinal metastases mostly concern the vertebral body. In the long bones, they are usually located at the diaphysis (Fon et al.).

Diagnosis is usually made by conventional X-rays, though Patten et al. state that CT revealed metastases in 12% of those patients conventional X-rays were 'blind'.

Spiegel et al. have observed six patients, 5% of their patients, where the spinal metastasis was the first or revealing sign of a MM. In their series of 114 patients with vertebral metastases, half also had bone metastases at other sites, most often in the ribs (29%).

Within the vertebral column, the thoracic segment is slightly more frequently involved, though multilevel

metastases are very frequent. The high frequency of the sacrum involvement is remarkable (table 14.51). There are no data according to the site of the primary.

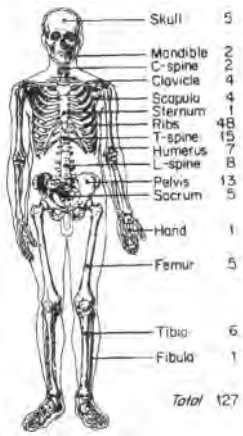

Fig.14.4 - Distribution of bone metastases in 50 patients with malignant melanoma (Fon et al., 1981, with permission)

Table 14. 51 - Malignant Melanoma
Metastases in the Vertebral Column (N=114)
Segment involved (Data of Spiegel et al.)

Cervical column	17.5%
Thoracic column	57.9%
Lumbar column	49.1%
Sacral segment	49.1%

The report of Donaldson et al., includes 15 patients with symptomatic spinal metastases. They observed about 3 locations per patient, with 60% of them at T12 or lower. Half of the patients had their primaries at the back, but correlation of this site with the lower spine was not made, as the specific site (upper or lower) was not given.

Gokaslan et al. have reported on 133 patients with metastatic spine. The thoracic (61%) and lumbar (64%) spine were the most frequently involved, while the cervical was involved in only 17% and the sacrum in 13%. In four patients, it was the first sign of a MM and in 32 (24%) of those with spinal metastases, the first metastases. Other skeletal metastases were detected in 57%. Their data on the radiological appearance are interesting (table 14.52). While the plain film is adequate for skeletal lesions proper, CT and MRI will provide more information to further delineate the pathology of the spine, including epidural masses, cord compression or intramedullary disease.
The relatively high number of spinal metastases in MM could be explained, at least partly, via the pathway described by Uren et al. They have described an unusual lymphatic drainage pattern from skin of the back, whereby the drainage proceeds directly through the posterior wall to the paravertebral lymph nodes. These nodes then can invade the vertebrae, similar to what has been described for lumboaortic nodes in cervical carcinoma and other primaries. In the series of Gokaslan et al., there were 57% primary lesions at the back, compared to 38% in other series. The authors, however, did not correlate the data with all the MM-patients treated at the institute. Some unusual metastatic sites have been reported (table 14.53).

Table 14. 52 - Malignant Melanoma
Spinal Metastases - Imaging Features
Data of Gokaslan et al.

	Plain film N=87	CT N=66	MRI N=58
Osteolytic	48%	86%	
Osteoblastic	9%		
Vertebral collapse only	28		
Soft tissue mass		26%	33%
Epidural disease		12	24
Leptomeningeal			14
Cord compression		1.5	10
Intramedullary			5
No abnormality	15	1.5	0

Table 14.53 - Malignant Melanoma
Unusual Bone metastases

Author	Patient	Primary	Metastasis	Interval
Stoler 1969	M48	???	Patella	??
Gelberman 1978	M24	Shoulder	Ri.thumb	4 yrs
Shin 1986	F84	Face	Sternum	2 yrs(')
Jaeger 1992	F65	Shoulder	Patella	Simult
Laredo 1998	M38	???	Sternum	??

(') at CT one can doubt about a retrosternal metastatic node invading the sternum

Gynecological Metastases

There have been several reports on MM metastatic to the ovaries. Most were symptomatic but there were cases who they were the first sign of a MM. So, a left adnexal mass in a F45 was the first symptom of a metastatic melanoma (Hsiu et al.).
Seven years after excision of MM at the back, a patient (F45) reported because of abdominal pain and a mass in the abdomen. Its metastatic nature was confirmed but she also had CNS metastases (Piura et al.).
Peritonitis following rupture of a metastasis in the ovary was the first sign of infaust evolution in a patient (F20) (Silveira et al.).

In 1987, Fitzgibbons et al. reported on 10 cases, of which 3 were found at autopsy. As could be expected, most had other metastases and developed further problems within the next weeks or months. The metastatic masses ranged in size from 4 to 22 cm, with an average of 11.4 cm. All tumors were encapsulated. Another personal series covering 18 cases was reported by Young et al. Bilaterality was noted in half of the patients. Large masses up to 20 cm, with a average of 10.5 cm were also observed. In most patients, the MM was evolutive.

We are aware of five reports on metastasis in the endometrium (table 14.54).

Reviewing the literature in 1992, Glaubitz et al. retrieved 9 cases (including their own case) and noted that the primary was located on the back in 4, at the lower extremity in 4 and at the cheek in 1. This metastatic site certainly needs more data.

Table 14.54 - Malignant Melanoma Metastases to the Endometrium Cases reported in the literature

Author	Pat	Site	Symptom	Interval
Pommerenke '89	F77	Calf	??	..
Takeda 1978	F74	Back	Metrorrhagia	??
Bauer 1984	F73	Leg	Metrorrhagia	Reveal
Nagy 1990	F38	Shoulder	Metrorrhagia	18 mo
Glaubitz '92	F65	Back	Metrorrhagia	14 mo

We are aware of only one case reported with involvement of the uterine cervix, even within a polyp. A F63 presented with vaginal bleeding about two years after having been treated for a MM on the lower leg (Bokun et al.).

Metastases to the breast have been reported in several publications. Cangiarella et al. could report on 7 personal cases. The size of the metastasis was relatively small, only 3 lesions measuring more than 3 cm. No preferential primary site was observed.
Previously, Arora et al. had reported on 15 patients, of whom 6, or 40% originated from a MM on the arm and 3 from the shoulder, obviously within the draining pathway. The MM was evolutive in almost all patients.
Two patients (F31 shoulder; F34 back) presenting with bilateral breast masses were reported by Majeski. In both patients, multiple other metastases were detected.
MM can present as a metastasized breast cancer. Barker et al. have reported on a woman (F42) presenting with skeletal pain and a large mammary tumor with widespread bone metastases. Immunohistochemistry at autopsy was able to provide the diagnosis of MM. This demonstrates the diagnostic pitfall of this masquerade.
At MRI, the appearance of metastatic MM in the breast is a high signal on T1W and low signal on T2W, with decreasing signal after intravenous contrast. According to Ho et al., this is specific to melanoma.

Metastases to the Placenta and the Fetus

The age of childbearing coincides to a certain degree with the peak age for MM, meaning that the incidence of MM is proportionally the most frequent malignancy in pregnancy.
There have been a large number of articles that have discussed the relation between pregnancy and melanoma, but it is most probably the coincidence of the age groups that is the most important reason for this high frequency, since a mutual influence has never been proved, except some incidental situations.
There is a definite risk of transplacental transmission of MM to the placenta and to the fetus.
MM is the most frequently reported malignancy with involvement of the placenta, about one-third of all cases. This indicates widespread hematogenous dissemination, and the high vascularity is a good reason for accumulation and growth of MM cells.
In about half of the MM cases, the fetus was also involved, but only a quarter of them will die of the malignancy, while the others will spontaneously 'heal'. Reports with a long follow-up are lacking.

Reviewing the literature in 1997, Baergen et al. retrieved 20s reported cases with placental involvement. The actual number of MM in pregnancy is of course unknown since not all placentas are scrutinized. Tumoral invasion can be very small as in their cases, since it was found in only 3 of the 50 microscopic sections. Another possible reason is that MM can be 'silent' during pregnancy after an earlier 'treatment'.

A very unusual case is that reported by Schneiderman et al. They reported on a newborn where a widely metastasized and fatal melanoma was recognized at birth, associated with metastases in the placenta, but the mother was still disease-free eight months after delivery.

Other Metastases

We are aware of three reports on metastasis in the testis. Richardson et al. reported on a M28 presenting with a testis tumor first diagnosed as a seminoma, but during its evolution recognized as a metastasis of a MM mass at the leg.
Three cases were reported by Datta et al. In two patients, the metastasis simulated a primary testis cancer, associated with large retroperitoneal lymph node metastases, but after further questioning, the patient revealed that a primary MM had been treated 16 and 3 years previously. Clinical details were not available for the third patient. Recently, a M44 was reported with a testicular metastasis 8 years after resection of a MM at the back (Ejadi et al.).

Pancreatic metastases from MM have hardly been discussed in the literature. We found a brief report on one case (F32), known of an advanced MM with a clear pancreatitis syndrome. Peri-ampullary biopsies proved the metastatic nature, apparently a diffuse infiltration of the pancreatic head and the duodenal wall (Sobesky et al.).

Adrenal metastases are not rare in MM. They amount to 50% at autopsy. Haigh et al. have reported on 83 patients referred for surgery for adrenal metastases from MM, from a database of 8,250 MM patients. Of the male patients, 75% were affected, but the gender distribution of the whole group was not given. The site of the primary was mainly 'non-extremity', but data were not adequately reported, in spite of its high

incidence, at least in autopsy series.
Adrenal metastases may be uni- or bilateral, with sizes ranging up to 6 cm. The appearance at CT is not specific. They present as round or oblong masses (Fishman et al.).
Hakenberg et al. have reported on a M70, in whom at staging for a prostatic problem, CT disclosed bilateral adrenal masses, metastatic from a MM excised from his back 16 years before.

Intramuscular metastases have been rarely reported, either by the patients unless painful or hindering or at autopsies, as they are almost never looked for. Yoshioka et al. have reported on a man presenting with a mass in the right thigh, 8 years after excision of MM at the cheek. CT could demonstrate a muscular metastasis in the right vastus lateralis. This is the only report on muscle metastases in MM. One intratendineous metastases, in the patellar tendon, was reported in a M41 four years after excision of a MM on the back (Silvestri et al.).

Sixteen months after excision of a MM at the right shoulder, a F56 reported with sudden onset of severe bilateral lower extremity pain, paraplegia, hypoesthesia and paresthesia in the lower half of the body. A bilateral femoral embolectomy was performed as vascular occlusion had been diagnosed. The source of the embols was most probably a metastatic mass in the lower pulmonary lobe (Harris et al.).

Reviewing 193 total-body CT in 53 consecutive MM patients, Patten et al. observed subcutaneous nodules in 17 or 38% of the patients. In 5 it was the only metastasis, while 85% had any metastatic site. These nodules appeared as small discrete rounded densities in the subcutaneous fat, most frequently in patients with MM at Clark's level IV or V.
The nodules were located in 56% in the region treated, but in 46% remote from the site of the primary. These data clearly suggest that such nodules are underreported finding, as the patients will certainly report any hindering or recently growing mass. They should then be found at clinical follow-up. Schwarz et al. have reported on 3 patients where subcutaneous nodules were the first sign of a metastatic melanoma.

A very rare metastatic site for any primary is the true intraneural metastasis. A patient (M50) treated about 5 years earlier for a retro-auricular MM presented with numbness along the postero-lateral part of his leg. MRI disclosed a tumor involving the sciatic nerve, confirmed as metastatic at surgery. Cantone et al. could only find four other reports on intraneural metastasis, all concerning a malignant melanoma, with involvement of the n.facialis, the n.vagus or the brachial plexus.

Acute multi-organ failure caused by rapidly progressing melanoma metastases is a very rare situation (Kaskel et al.).

'Very Late' Metastases

Several reports have dealt with late metastases. While is not uncommon in other cancers, it has received much more attention in MM. A very late metastasis is defined as with an interval of more than 10 yrs.
Crowley et al. found 168 patients from one institution or 2.4% from a group of 7,104 patients.

However, they did include the ocular melanomas (12 patients). More than 90% of the patients were treated at stage I. No difference according to gender, age or primary site could be observed between the early and the late recurrence group (table 14.55). The large number of liver metastases in ocular M is what one would expect.

Table 14. 55 - Malignant Melanoma
Very Late recurrences - Site according to Primary Site
Data of Crowley et al. (N=168)

	Primary Site			
	Extremity	Trunk	H&N	Ocular
	N=67	N=67	N=21	N=12
Local	10.4%	10.4%	14.3%	8.3%
Nodes	59.7	38.8	23.8	--
Dist.skin	3.0	4.5	9.5	--
Lung	11.9	20.9	19.0	8.3
Liver	3.0	--	4.8	66.7
CNS	1.5	6.0	--	--
Other	10.4	19.4	28.6	16.7

Causes of Death

Due to the high frequency of pulmonary involvement, respiratory failure is the main cause of death. The second main cause is complications of the CNS, mainly due to parenchymal metastases. Cardiac failure will either have a metastatic cause or be secondary to the pulmonary involvement (table 14.56).

Overall Lesson

MM has a widespread metastatic pattern, with a high incidence of lung involvement, liver, adrenal and heart, though all the other organs can be involved. Any unusual symptom, even years after first treatment, should raise suspicion of a metastatic process.

Table 14. 56 - Malignant Melanoma
Causes of Death (N=216)
Data of Patel et al.

Respiratory failure	39.4%
CNS complications	19.9
Cardiac failure	10.2
Liver failure	6.9
Infection	6.5
Renal failure	1.9
Adrenal failure	1.4
Miscellaneous	13.9

METASTASES from MALIGNANT TUMORS of the LARGE VESSELS

Malignant tumors of the large vessels are rare. Previously mainly detected at autopsy, the present diagnostic armamentarium certainly allows earlier diagnosis of this uncommon malignancy. They have an insidious course and several presented as a misleading pathology or with uncommon metastastic sites. Histologically, the tumors are of the sarcoma-type, mainly angiosarcomas, but other types will also present.

METASTASES from MALIGNANT TUMORS of the AORTA

Reports of cases of malignant tumors of the aorta are rare. Khan et al. could retrieve only 37 case reports for their review in 1997.
Three different pathology presentations have been observed, as was delineated by Wright et al. (fig.14.5). The first involves the intima and presents with symptoms related to thromboembolic metastases, mainly in the intestine as mesenterial emboli. Tumors originating or situated in the adventitia or media are locally aggressive masses with limited or no metastases, unless the intima is involved.
The symptomatology in the latter group is more vague, and consists of anorexia, malaise, fever and weight loss.

Tumors at the intima may be either non-obstructive or obstructive. They are the most frequent type, tumors originating at the wall or mural being relatively rare.
The location of the tumor in the aorta will determine the metastatic behavior and symptomatology. The primary may extend through the aortic wall, with intraluminal extension to the renal and iliac arteries. Involvement of the terminal ileum and colon will lead to infarction and even mucosal ulceration of the rectum.

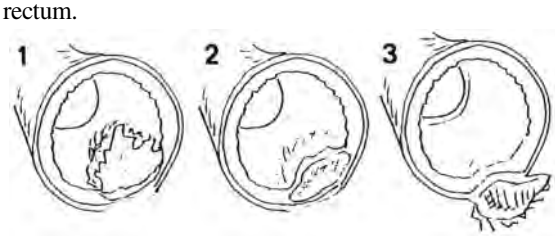

Fig.14.5 - The three different pathologies of vascular tumors: 1. originating from the intima; 2. from the media; 3. from the adventitia.

Two clinical patterns of presentation have been observed, acute distal embolization or acute hypertensive crisis. Located above the arteria renalis, they will usually present with hypertension concomitant with tumor embols in the renal artery. When situated lower, they will either present with mesenterial emboli or in the lower limb (see further fig.14.6). The rare more central ones can manifest themselves through cerebral emboli or in the upper limbs. Other metastatic sites as bone, skin and lungs should, however, not be excluded.

Table 14. 57 - Aortic Sarcoma
Selected Literature Case Reports

Author	Pat	Complaint	Site	Diagn.
Winkelman'71	M56	Both legs	Abdominal	Imaging
Patel 1976	F60	Femur Tibia	Thoracic	Autop
Mason 1982	M70	Mid-abd.pain	Abdominal	Imaging
Schmid 1984	M75	Aort Occlus.	Thoracic	Autop
Wright 1985	F46	Bowel infarct	Abdominal	Autop
Guyton 1987	M64	Abdomen	Abdominal	Surgery
Bryan 1988	F66	Thigh pain	Abdominal	Autop
Herzberg '88	M75	Heart Fail	Thoracic	Autop
Josen 1989	M75	Pain leg	Thoracic	Surgery
Fitzmaurice'90	M67	Abd.Pain	Thoracic	Autop
Fusade 1991	M68	Skin back	Abdominal	Surgery
Higgins '91	M65	Bowel infarct	Thoracic	Surgery
Tejada 1991	M69	Popliteal	Thoracic	Surgery
Kunkel 1993	M59	Bowel Tum	Thoracic	Autop
Bertucci '95	F72	Thigh pain	Thoracic	Surgery
Ruijter 1996	F73	Mesenteric	Thoracic	Autop
Khan 1997	M62	Pain leg	Abdominal	Surgery
Daniel 1997	F73	Thigh	Abdominal	Surgery
Daniel 1997	M56	Pain L2(')	Abdominal	Surgery
Ingelholm '97	M82	Back - Skin	Arch	Autop
Becquemin '88	M67	Skin nodules	Distal	Surgery
Seelig 1998	M71	Skin LL	Thoracic	Surgery
Clark 1998	M76	Embols LL	Abdominal	Surgery
Miracco 1999	M68	Chest pain	Abdominal	Pathol.
Iorgulescu '99	F57	Chest pain(°)	Abdominal	Surgery
Mohsen 2000	F48	Hemiparesis	Arch	Autop
Rudd 2000	M59	Skin nodules	Abdominal	Surgery

(') bone osteolysis, later also pulmonary; LL.: lower leg
(°) later pleural, nodes, muscle metastases

The embolic events constitute the acute presentation of these tumors, and will mimic diverse more common conditions as dissecting aneurysms, acute abdomen situations, peripheral arteriosclerotic diseases and abdominal or retroperitoneal masses. As primary tumors, they must be differentiated from the more common cardiac myxomas with peripheral embols, but also from bronchial and other cancers. Clinical judgment and optimal vascular and systemic imaging are very important in the diagnosis of this most misleading tumor.
The terminology of the histology is confusing, as the terminology of the 'malignant' sarcomas is rather polymorph, so that terms of fibrosarcoma, spindle cell, myxosarcoma, angiosarcoma and pleomorphic sarcoma, and recently malignant fibrous histiocytoma have been used.

A selected list of case reports are in table 14.57. All patients presented with symptoms that could be ascribed to a metastatic process, but masquerading as a more common clinical situations such as embolic events in the leg and the abdomen. There are also cases presenting with skin lesions and bone osteo-

lysis, all misleading the most advertant clini-cian. Not even CT of the abdomen can be relied up to detect any aortic 'abnormality'.

Distant Metastases

Reviewing the literature on aortic sarcomas in 1998, Seelig et al. found 87 cases reported since 1873. Metastases were reported in 51, or 58.6%, of the cases. In 12 cases or 20.3% no metastasis were observed. In general, metastases were observed in bone (28.8%), the kidneys (27.1%), the liver (23.7%), the adrenals (20.3%) and the lungs (15.3%).
An earlier review by Fusade et al. (1991) mentions metastases to the skin, muscle, spleen, the intestine and the peritoneum. They found reports dealing with mesenterial, limb and bone embolism.

As revealing metastasis, Fusade et al. mention a patient with discrete skin erythemic lesion, in whom the pathologist disclosed angiosarcoma features. Previously, a case presenting with rectal metastases had been reported by Winkelman et al. The case reported by Becquemin et al. also presented first with an increasing number of cutaneous nodules, only months later disclosed as metastases from an aortic sarcoma, after a clinical diagnosis of embols in both iliac arteries.
There is no doubt that this is a very enigmatic tumor that can mislead every oncologist, vascular surgeon or emergency doctor.

METASTASES from MALIGNANT TUMORS of the LARGE VEINS

The malignant tumors of the large veins are predominantly leiomyosarcomas.
The most frequent site, in about 75% of cases, is the abdominal or lower vena cava, but a few cases of the superior vena have also been reported. Spaggiari et al. reported on a M52 who, after a long remission after various recurrences, developed eventually metastases in the right triceps muscle. Other cases have been located in the peripheral limbs. Half are still only diagnosed at autopsy, in spite of modern diagnostic possibilities, but probably because of the misleading symptomatology.
Within the inferior caval vein, the middle third at the height of the renal vein is the most frequently concerned, either isolated (28%) or combined with another third (18%).

Symptoms may be absent as the a number of incidental and autoptic discoveries shows. There is some relation between the site of the tumor and the clinical manifestations. Most patients will have a long story of progressive dull pain in the lower limb and lower back, with vague abdominal complaints, malaise and weight loss. Progression of the tumor is associated with thrombotic events, so that other common pathological conditions will occur and mislead the clinician. Cases with Budd-Chiari syndrome, thrombosis of the renal and pelvic veins, pulmonary embolism and tumor thrombus extension up to the right atrium have also been reported.

Metastases as first presentation have been observed in the skin, the liver, the lungs, cervical nodes, brain and bone (review by Sturm et al.).
Sixteen cases were reviewed by Burke et al. They observed 7 cases with distant metastases, involving mainly the lung and the liver, but adrenal, renal, pleura, skeletal and nodal metastases were also found.

The most recent review dates from 1997 by Kulaylat et al. They retrieved 130 cases from the literature. In one third, the diagnosis was only made at autopsy. Metastases were reported in 16 patients. About half of the patients had the dreaded tumor thrombus with multiple extensions up to the right atrium. Some of the metastases described can, however, be ascribed to contiguous invasion, for example within the stomach and the pancreas, from the caval tumor out.
The leiomyosarcomas in the peripheral veins are frequently complicated by pulmonary metastases. Of the 6 cases reported by Berlin et al., all developed fatal lung metastases.

METASTASES from TUMORS of the PULMONARY ARTERY

These tumors are rare, but apparently twice as frequent as the primary aortic sarcoma (Raaf et al.). Pulmonary artery sarcoma almost always developed in the main pulmonary artery and extends into the pulmonary artery branches or proximally into the pulmonic valve, the opposite pulmonary artery or right ventricle. When detected, about 50% wil be confined intravascularly, but the other 50% will have transmural extension into adjacent lung parenchyma, bronchi or lymph nodes. Distant metastases have also been observed (Rafal et al.).
The tumors have a polypoid appearance with a more or less pronounced obliteration of the lumen. The actual sites of the tumor was reviewed in the cases reported up to 1980 by Bleisch et al. (Table 14.58).
At histology, the leiomyosarcoma are in the majority.

Table 14.58 - Sarcoma of the Pulmonary Trunk
Location of the tumor (N=60)
Data of Bleisch et al.

Pulmonary Valve	57%
Right Outflow	25%
Ricght Pulmonary Artery	67%
Left Pulmonary Artery	60%
'Heart'	37%

Symptoms are insidious and include dyspnea, chest

pain, cough and syncope and delaying correct diagnosis. The most usual pattern is a right heart failure due to multiple pulmonary tumor emboli (Table 14.59). Previously, the majority were only detected at autopsy, though many are inoperable due to the extensive destruction of the neighbouring structures. Furthermore, several have already distant metastasis.

Table 14.59 - Sarcoma of the Pulmonary Trunk
Presenting Features in 60 reviewed Cases
Data of Bleisch et al. 1980

Symptoms		Findings	
Dyspnea	70%	Systolic murmur	56%
Chest Pain	48	Diastolic murmur	7
Cyanosis	36	RVH on ECG	35
Cough	34	X-ray large heart	39
Edema	32	X-ray hilar mass	39
Hemoptysis	30	X-ray enl. pulm.art.	25
Syncope	25	X-ray decr.pulm.vasc.	23

One particular case had invasion of the bronchi, as was diagnosed by means of an endobronchial biopsy. Within a few months, there were also metastases in the tongue, the skin and the pleura (Balduin et al.).
Chest radiology will show aspecific features such as hilar mass, peripheral infiltrates, enlargement of the central pulmonary artery and decreased vascular markings, as may be observed in pulmonary embolism.
Ventilation-perfusion radionuclide scan is as aspecific, showing either massive obliteration of one artery suggestive of pulmonary tract outflow obstruction or smaller embols.
Two-dimensional and/or transesophageal echocardiography should play a more important role in diagnosis, as well as CT and MRI.

Distant Metastases

Reviewing 93 cases of pulmonary artery sarcoma from the literature, Ramp et al. were able to note several unusual sites of metastases, out of the pulmonary (61%). They occurred in 19% of the reported cases (Table 14.60).

Table 14. 60 - Pulmonary Artery Sarcoma
Distant Metastases (Non-Pulmonary)
Literature Review by Ramp et al. 1992

Brain	3 cases	Peritoneum	1 case
Thyroid	1 case	Adrenal	3
Tongue	1	Kidney	1
Sternum	1	Pancreas	1
Pleura	4	Jejunum	3
Diaphragm	3	Skin	1

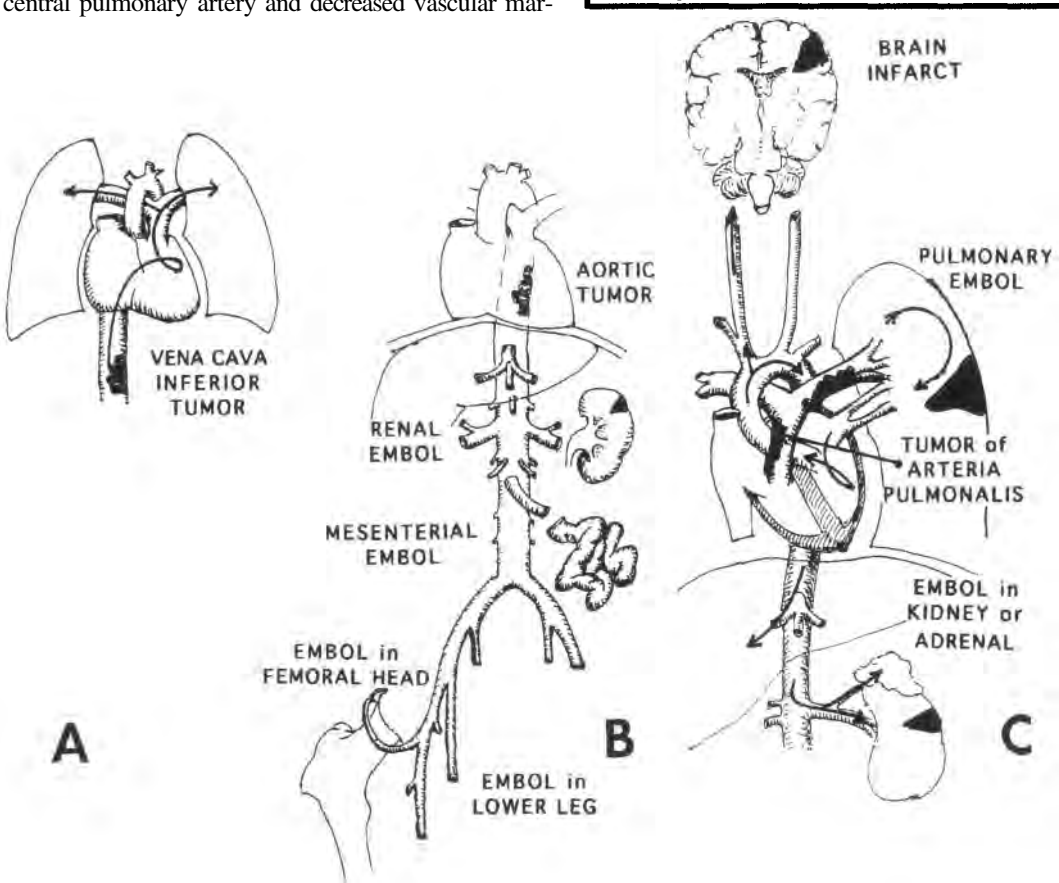

Fig.14.6 - Comparative anatomoclinical features of Sarcomas of the Vena Cava Inferior (A), Sarcomas of the Aorta (B), and Sarcomas of the Pulmonary Artery (C)

Table 14.59 - Sarcomas of the Large Vessels
Comparative Features
Modified from Brochériou et al.

Feature	Aortic	Pulm.Art.	Inf.Vena Cava
Mean age	62 yrs	41 yrs	50 yrs
Ratio M/F	1	3/1	1/3
First Sy	Syst.Embol.	Pulm.Emb.	Pelvic pain
	Leg pain	Dyspnea	Thrombotic
Histol.	Int.Sarc 73%	Int.Sarc.88%	Int.Sarc. 6%
	AngioS. 18	AngioS. 6	
	LeioM 9	LeioM 6	LeioM 94

Eisenmann et al. reported on a man (M39) presenting two years after curative surgery with a local recurrence, associated with a large omental metastasis. The features of the three different sarcomas of the large vessels have been collated in table 14.61 and fig 14.6.

There have been also descriptions of malignant tumors of the pulmonary veins. Extension towards the left atrial cavity is common in these tumors. But, as most leiomyosarcomas of the heart originate in the left atrium, it is most probable that they will be atrial leiomyosarcomas extending back to the pulmonary vein (Babatasi et al.).

METASTASES from OSTEOGENIC SARCOMA

Osteogenic sarcoma or osteosarcoma is characterized by malignant deposition of osteoid with varying amounts of mineralization, cartilage and fibrous tissue. The resulting typical radiological appearance is that of permeative or irregular areas of bone destruction with adjacent bone formation showing varying degrees of mineralization. This appearance is maintained by a majority of the distant metastases, resulting in a detection possibility by plain radiograph and by radionuclide bone scintigraphy. The latter can even detect ossifying metastases unrecognized and undetected by chest radiograph or CT (Brady et al.).

Osteosarcoma can arise anywhere in the skeleton. The most frequent site of the primary is 'around the knee', accounting 60% of the cases in the series of Uribe-Botero et al. Overall the femur accounts for 50% of all primaries. The distribution in their series of 243 cases is depicted on fig. 14.7.
Apart from local evolution, destruction and invasion, osteosarcoma metastasizes predominantly through the hematogenous route, most frequently the lungs, as they are the first capillary bed encountered by the migrating cells. A rarely encountered spread that by lymphatic migration to regional nodes.

There will be direct contact of the primary osteosarcoma with blood vessels, which can cause local thrombosis with growth of tumor cells within them. The synovial membrane seems to be a particular 'guide-way' for malignant cells to penetrate into the peri-articular space, but also within the articular cavity and adjoining bone.

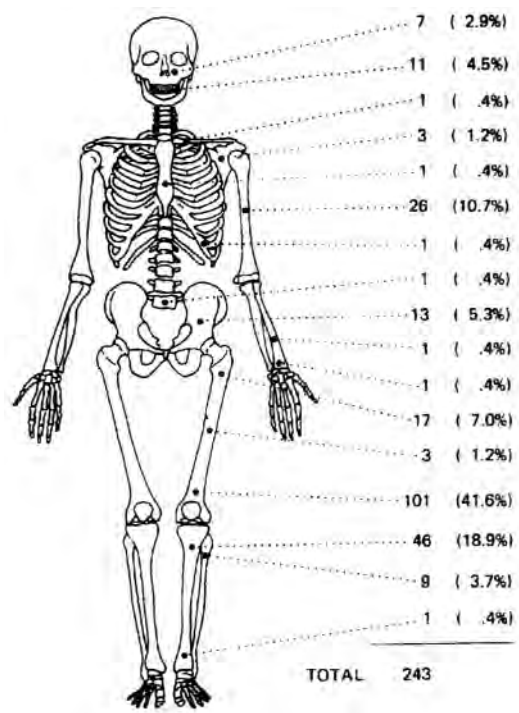

Fig.14.7 - Distribution of the Primary Site in 243 cases of osteogenic sarcoma. (Uribe-Botero et al.,with permission)

Biopsies or surgical incisions also provide the opportunity for malignant cells to seed within the articular space and periarticular tissues. These metastatic pathways outlined by Campanacci et al. are shown in fig.14.8.

Pattern of Distant Spread

Complete and adequate data on 135 cases (mixed clinical/autopsy) have been published by Jeffree et al. The publication dates back to 1975. It should be worthwhile to have more recent data, particularly to gain an insight on the influence of intensive chemotherapy as is nowadays administered, but also as the detection possibilities have increased dramatically.

Of 124 patients, 91 (73%) had clinically evident lung metastases (LM) and 30 (24%) had clinically evident extrapulmonary metastases (EPM). Both types of metastases were present in 23 or 19%, leaving 61% with LM only and 7 or 5% with EPM only. The data on Fig 14.7 shows the high frequency of lung metastases and a frequency of less than 5% in every other site documented.

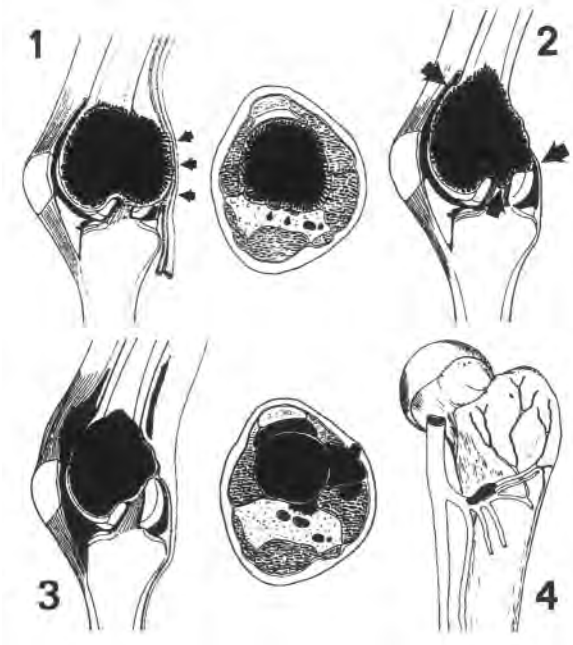

Fig.14.8 - Local anatomical factors predisposing to further spread of malignant cells in osteosarcoma. 1. Close contact with vessels with merging of the pseudocapsule and the adventitia. 2. Progressive involvement of the synovial membrane. 3. A hematome, either accidentally or after surgery, will predispose to a contamination of the articular cavity. 4. Tumor cell thrombus in an efferent vena (From Campanacci et al., with permission)

Lymph Node Metastases

In all standard textbooks, it is claimed that sarcomas metastasize only along the vascular system. Over the years, however, reports have appeared in patients with osteosarcomas on regional and even distal as mediastinal and retroperitoneal lymph node metastasis. Reviewing the charts of 182 patients treated by radical surgery, Caceres et al. found an incidence of 10.4% involved regional nodes. This clearly demonstrates that lymph node involvement is not rare. In fact the data from Jeffree et al. also mention 10% regional lymph node metastases in the 29 autopsied cases and only in 3% of the clinical records.
Ossified mediastinal nodes are not uncommon in patients with widely metastatic disease (Johnson et al.).

Pulmonary Metastases

Common early in the course of disease, pulmonary metastases heve been seen in 75-85% of the patients. The metastases will vary in size ranging from miliary nodules to the typical 'cannon-ball' masses. Most, however, are smaller than 3cm, while some very large lesions have been noticed.
At radiology and certainly at CT, they will be frequently calcified, either diffuse or eccentric. This poses a problem of differential diagnosis, as some benign lesions and rarely metastases from other primaries also can present with some calcifications. Vanel et al. observed them in 193 metastases, out of a total of 32 patients, with a range of 1 to 65 per patient. About half of the metastases were located subpleurally and the other half in parenchymes.

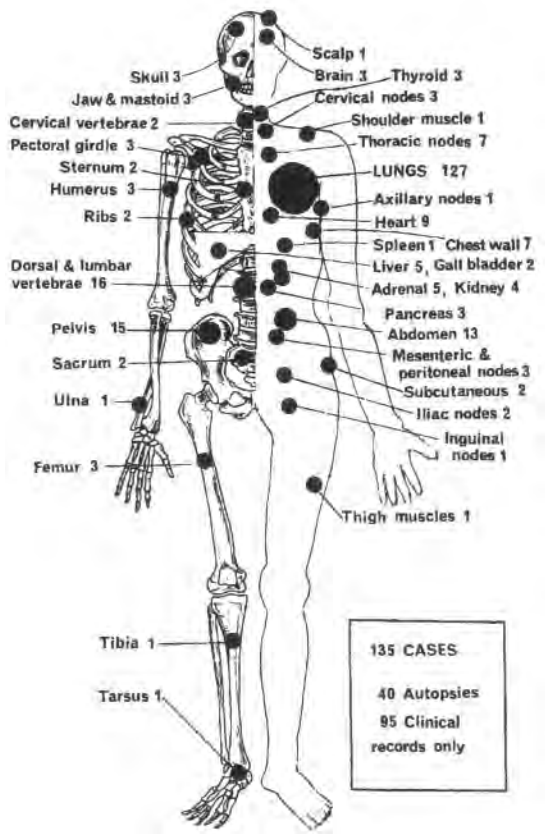

Fig.14.9 - Overall pattern of metastases of osteosarcoma to bone and soft tissue (Jeffree et al., with permission)

Cavitation of the nodule is uncommon, while in 5%, spontaneous pneumothorax has been observed, particularly when localized subpleurally (Johnson et al.). Yamamoto et al. have reported on a spontaneous pneumothorax occurring in a 11-year old girl, simultaneously with the tumor in the distal femur. There were no visible pulmonary metastases, though the author admitted the possibility of microscopic metastases. Congenital bullae are another possibility. Spittle et al. where able to report on 4 cases, all children, and reviewed the literature at that time (1968), retrieving 16 other cases.

As is usual in the literature, there are virtually no data on the pathology of the pulmonary metastases, in spite of the large surgical series reported. A few data have been found in these series, but they are certainly biased towards operability (table 14.62).

Table 14.62 - Osteogenic Sarcoma
Pathology features of Lung Metastases (N=206)
Data of Briccoli et al.

Unilateral	145 (70%)
Bilateral	61 (30%)
Number 1	85
2-3	61
4-5	26
>5	34

Of 111 consecutive patients, 53 or 47.4% developed pulmonary metastases, with a follow-up of minimum 1 year (Ward et al.).
As far as the data of Ellis et al. are representative, it seems that the tibial osteosarcoma has a higher propensity to metastasize than other sites (table 14.63). The data of Uribe-Botero do not confirm this trend, but more data should be made available.
As far as metastatic site within the lungs is concerned, Antunes has reported some data (Table 14.64).
Remark the lower incidence in the right upper lobe, but more data are needed for valable conclusions.
Endobronchial metastases have been reported twice from bone osteosarcoma (Bolliger et al., Mogulkoc et al.). Kiryu et al. have recently added two cases (M15, tibia and M24, femur). In both, it concerned an endobronchial extension of a large mass seen at thoracotomy. This is probably an underdiagnosed metastasis.

Table 14.63 - Osteogenic sarcoma
Frequency of Lung Metastasis and Primary Site

	Ellis		UribeBotero	
	N	With	N	With
Femur	21	14.3%	121	26.5%
Tibia Fibula	16	31.2	47	21.2
Pelvis	8	25.0	--	--
Humerus -Other	11	18%	26	30.7

Table 14.64 - Osteogenic Sarcoma
Site of Pulmonary Metastases (N=321)
Data of Antunes et al.

Right Lung		Left Lung	
Upper lobe	13	Upper lobe	31
Middle lobe	6	Lower lobe	32
Lower lobe	31		

Massive pulmonary tumor emboli from osteosarcoma have been reported in seven cases. Almost all were of the chondroblastic type, joining the propensity of chondrosarcoma for this type of metastases. Four originated from the femur, being the most frequent primary site (Ahmed et al.).

We want just to mention the study of Jaffe et al., who demonstrated that chemotherapy (1983) did not lower the number of pulmonary metastases, but effectively retarded their appearance from a median time of 7 to 17 months.

Skeletal Metastases

There has been a decade-long discussion if the 'other' sites involved were multi-focal osteosarcomas or true metastases. Some patients presented indeed with multiple bone sites involved. The arguments produced by Daffner et al. seem to have settled the discussion.
Several authors have reported small series of multifocal metachrone osteosarcomas (Fitzgerald et al.; Mahoney et al., Thayer et al.).

In amputation pieces, pathologists have observed the presence of the so-called skip metastases. They are foci of osteosarcomas separated from the primary lesion by several centimeters and are the probable source of local recurrence when the amputation margin was too conservative (Enneking et al.). Skip metastases can now clearly be demonstrated with modern imaging methods.

The multicentricity of several cases of osteosarcoma and even the very wide involvement of the whole skeleton, sometimes in the absence of pulmonary metastases has resulted in several discussions and hypotheses. The current theory is that these situations are the results of widespread metastasis along the plexus of Batson.

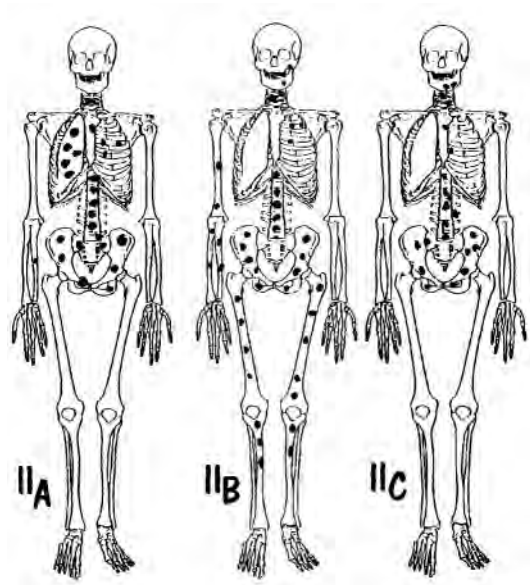

Fig.14.10 - Osteosarcomatosis type II according to Ippolito et al.

Osteosarcomatosis

One particular form of multifocal or multicentric osteosarcoma or osteosarcomatosis is the extremely diffuse metastatic or miliary spread of the malignancy (Chap et al.). Only a few cases should have been reported. The lesions typically involve the metaphyseal sites. Individually they all resemble classic osteosarcoma, but one large dominant lesion is always

found, in fact the primary site. The distribution of the sites apparently follows the drainage pattern of the vertebral venous system of Batson. They present as a myriad of small lesions without soft tissue involvement.

Presenting one case and reviewing all reported literature cases, Ippolito et al. proposed a clinical classification of the syndrome (table 14.65; fig.14.10), based on the previous one of Amstutz, but no longer valid in view of the different cases reported. Previously, Hopper et al. had already concluded that the Amstutz classification was not appropriate.

Table 14. 65 - Osteosarcomatosis
Clinical Classification proposed by Ippolito et al.

	Skeletal	Spread
I Radiated Pauciful Synchron	Multiple in irradiated sites	General circulation
II Nonradiated Miliary Synchronous	A. Axial + lungs >30 lesions	Batson + gen.circulation
	B.Axial + areas distal to elbow/knee	Batson + skip meta
	C. Axial (Batson) usually >100	Batson only
III Pauciform		
A.Metachronous	Classical sites successive	General circulation
B. Synchronous	Classical sites <30 lesions	General circulation

The patients usually present with diffuse variable pain and a marked anemia, sometimes thrombopenia and hypocalcemia. According to Hopper et al., its incidence is about 4.2% of all osteosarcomas.

Brain Metastases

Metastases to the brain are not common. A few cases have been reported, but there are probably many more, enclosed in the data banks of multi-institutional trials as the series of Marina et al. would suggest. A few have been reported as revealing, where the primary was evident 'at first look' (table 14.66).

A series of 13 patients with brain metastases have been reported by Marina et al. They observed an incidence of 5% (13/254) in their entire series of treated osteosarcomas. Only 3 were female patients and the primary was at the femur in 7. The other primaries were at the humerus (4) and the tibia (2). Six patients had other metastases, either in the lung or/and bone.

Brain metastases were more often seen in patients with pulmonary and/or bony metastases (6/46 or 13%) than in those with localized disease (7/208 or 3%). The brain metastases also developed more frequently in patients with first recurrences within one year after initial treatment (Marina et al.).

Table 14.66 - Osteosarcoma
Brain Metastases reported in literature

Author	Pat.	Primary	Site of M	Interval
Danziger 1979	F20	Ri.Femur	Occip.Temp.	Simult
Danziger 1979	F15	Ri.Femur	FrontoPar	33 mo
Danziger 1979	F18	Ri.Femur	Parietal	6 mo
Newamn 1987	M19	Femur(?)	Cerebellum	2 yrs
Baram 1988	M15	??	Pariet+Occip	46 mo
Baram 1988	F11	??	??	2 mo
Baram 1988	M12	??	??	12 mo
Baram 1988	F8	??	Frontal	17 mo
Baram 1988	F14	??	Frontal	9 mo
Arrington '90	M21	Femur	Ri.Occipital	1 yr
Kincaid 1992	M19	Le.Humerus	Occipital	8 mo
Marina 1993	M3	Le.humerus	Temp+Pariet	3 mo
Menassa 1997	M12	Le.Fibula	Par+Front	Simult
Moussa 1997	M15	Ri.Fibula	Temp+Front	Simult
Peh 1999	M20	Humerus	Thal+Cerebell	14 mo
Ogose 1999	M52	Le tibia	Parietal	--
Ogose 1999	F14	Le.Femur	Temporal	2 mo
Ogose 1999	F11	Ri.Femur	Multiple	12 mo

Metastases to the Head and Neck

Primary osteosarcomas at the skull and mandible and maxilla are rare. Metastases to the region have been reported in a few cases (table 14.67).
Snyder et al. mention five other cases reported before 1967, but further details were not available.

Table 14.67 - Osteogenic Sarcoma
Metastases to the Head and Neck

Author	Pat	Primary	Site	Interv.
Snyder 1968	M14	Ri.Femur	Mandible	4 mo
Ohba 1975	F17	Le.fibula	Mandible	1 yr
Singh 1978	M11	Ri.Femur	Maxilla	??
Shimizu '94	M51	Ri.Tibia	Larynx	10 yrs
Suzuki 1999	M22	Femur	Mandible	4 yrs

Abdominopelvic Metastases

As fig.14.7 demonstrates, osteogenic sarcomas can metastasize within the abdominal organs. Any abdomino-pelvic complaint, even several years after initial treatment, should raise suspicion of it being related to a metastatic process, in spite of the fact that lung and bone are the most frequent metastatic sites.
The reported cases have been collated in table 14.68. They clearly show the variable nature of the presentations. Most of the metastases were described as massive tumors, with a primary almost always located in the femur.

Other Metastases

Possibly due to today's more efficient chemotherapy, some peculiar metastases have been reported.
Recurrent multiple and calcified soft tissue metastases spread over the trunk and the extremities occurred in a man over a period of 18 months. Among other sites, he developed later also peritoneal metastases (table 14.68). This patient never had pulmonary metastases

(Wolf et al.).
Peh et al. have reported on two patients presenting 1 and 2 years after initial treatment with various different muscle masses diagnosed as metastatic osteosarcoma. Another case was reported by Miki et al. on M21 who developed several muscle metastases in all limbs and in the trunk during the course of half a year.

Table 14. 68 - Osteogenic Sarcomas
Abdomino-pelvic Metastases Reported

Author	Pat	Primary	Site of M	Interval
Hallet 1984	F13	Ulna	Le.Kidney	14 yrs
Rubin 1985	F66	Femur	Pancreas	3 yrs
DeJong 1985	M15	Tibia	Ri.Kidney	6 mo
Heinle 1989	M17	Femur	Peritoneum	24 mo
Balingit 1994	F16	Femur	Le.Kidney	3 yrs
Glass 1996	F9	Femur	Pancreas	7 mo
Glass 1996	F14	Femur	Pancreas	5 yrs
Raby 1996	F21	Femur	Ri.Kidney	3 yrs
Eltabbakh '97	F23	Humerus	Ri.Ovary	7 yrs
Westra 1998	M19	Femur	Peritoneal mass	28 mo
Costa 1998	M18	Femur	Periton.+Liver	19 mo
Wolf 1999	M24	Femur	Peritoneum	3 yrs
Peh 1999	M20	Humerus	Adrenal, Stomach, Peritoneum,pancreas	2 yrs

Stavrakakis et al. have reported on a patient (F54) who presented 3 months after amputation with multiple subcutaneous nodules which at histology were found to be metastatic from an osteosarcoma.
Previously, Setoyama et al. had reported on a patient (M20) with a metastatic lesion at the scalp 3 years after treatment of an osteosarcoma of the femur. Newman et al. reported a patient with metastasis in the upper eyelid, 3 years after initial treatment. Another case (M21) with lymph nodes infiltrating the skin in the neck was reported by Myhand et al. A biopsy disclosed metastatic osteosarcoma from a clavicular tumor, first thought to be a recurrence of his Hodgkins disease.

Cardiac metastases are not uncommon, as fig. 14.9 demonstrates. In 1966, Dorfman et al. reported on 4 cases certified at autopsy. One had an inferior vena cava thrombus extending from the amputation stump up to the right atrium and another had a metastatic mass at the mitral valve. The other two had extensive ventricular involvement.

The involvement of the heart can be very extensive, with the heart being progressively encased in a 'calcified' armour, seriously limiting the motility and the functionning of the heart (Seibert et al.). Pakter et al. described a case presenting with esophageal obstruction due to a massive pericardiac and mediastinal metastatic osteosarcoma mass. In a 31 year old woman complaining of backache, a mass in the left atrium was found, which showed to be at surgery a neurilemmoma. New metastases developed and at autopsy, a large sacral plexus tumor was found retroperitoneally (Ishikawa et al.).

A case (F9) with mesothelioma-like pleural encasement metastatic to a femoral osteosarcoma was reported by Shanley et al. An extensive mediastinal nodal mass occurred in a M15, 14 months after initial treatment (Charig et al.).

Danziger et al. mention in the report that their third case (brain metastases) also had metastasis in the breast and intraspinal extradural deposits.

Four years after surgery for an osteosarcoma at the tibia, abdominal pain occurred in a M21. Surgery disclosed metastases in the wall of the jejunum and another in the ileum, presenting like polyps (Panizo-Santos et al.).

Sarcomatous tumors are known to frequently cause massive and fatal pulmonary tumor emboli. Two patients have been described in detail. They had a long hisstory of several excisions and finally died by tumor embols, confirmed at autopsy (Wakasa et al.).
A metastatic mass from an osteosarcoma of the right iliac bone was found at autopsy encroaching the bifurcation of the aorta and forming a source of femoral arterial embolism in a man aged 53 operated a few days previously (fig. 14.11) (VanWay et al.).

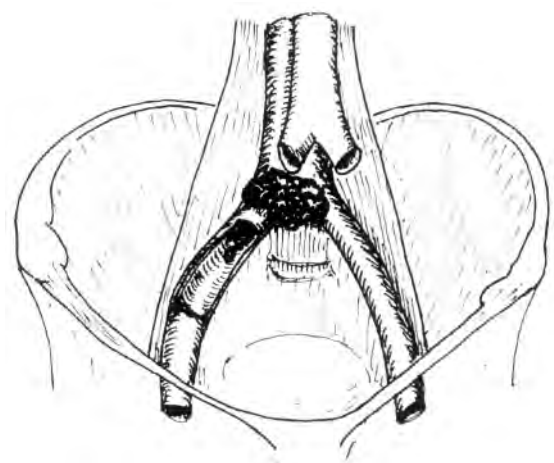

Fig.14.11 - Illustration of a sarcoma encroaching on the bifurcation of the aorta and complicated by intra-arterial iliac tumor embol.

METASTASES from CHONDROSARCOMA

After osteosarcoma, chondrosarcoma is the second most common malignant solid tumor of bone. Three quarters of the chondroid tumors consist of 'conventional' chondrosarcomas, while the other ones are labeled as variants. At histology, a grading from borderline to high can be observed. More than half of the cases originate in the limbs.

Distant metastases occur mainly in the lungs. Local relapse is a major factor in the incidence of distant metastases, but only in grades 2 or 3 (Ozaki et al.). The size and location of the primary have no influence. The pulmonary metastases may be single, but they are usually multiple and large.
Leung et al. have reported on a patient (F22) presenting at emergency with pain at the bony pelvis and with sudden shortness of breath. Urgent open-heart surgery revealed a beaded mass within the inferior vena cava through the right atrium and right ventricle. Histology disclosed the chondrosarcoma, similar to that of the iliac crest obtained afterwards by percutaneous biopsy.

The rarity of chondrosarcoma precludes mapping of an overall pattern, but skeletal metastases are apparently second in line to those of the lungs, in spite of the fact that several patients have been observed with skeletal metastases in the absence of pulmonary involvement (Disler et al.). The latter is difficult to explain, unless one hypothesizes that there is destruction of metastatic cells in the lungs, with some passing through to the general circulation, or most probably Batson's way. As primary sites have not been mentioned, it is impossible to reach conclusion.
The main sites for skeletal metastases are the spine, skull and ribs.
Brain, liver and kidney metastases are mentioned in some series.

Cutaneous Metastases

Arce et al. state that skin metastases are as frequent in chondrosarcomas as in other primaries. Presentation as initial manifestation is even rarer. The authors reviewed the literature and could retrieve 10 other cases of skin metastases. Most arise from chondrosarcomas at the extremities. While most metastases are single, several multiple have been reported. The mean interval between primary diagnosis and observation of metastases is 46 months, or nearly three years, but within a range of 1 to 10 years. The site of the metastases is ubiquitous, from scalp to thumb, from vulva to nose. In two patients, simultaneous gingival lesions were observed.

Cardiac Metastases

Reporting on a patient with cardiac metastases as first presentation, Fichaux et al. found 20 other reports in the literature. The site was the right heart in 13, and at the left in 7. Most cases had simultaneous involvement of the atrium and ventricle. Pulmonary metastases will always be present, so that extension to the heart occurs either along the pulmonary veins or retrograde by tumor thrombus to the right.
Cohen et al. have reported on metastatic involvement of the left atrium in a M22, 5 years after amputation of the tibia(?). A large lower pulmonic mass was noted, obviously the source of this uncommon metastatic site. A fatal pulmonary tumor embolism from an iliac chondrosarcoma (M12) was reported by Soares et al.

Other Metastases

Okano et al. have reported on a patient (M66) presenting 6 years after resection of a costal chondrosarcoma with pulmonary hypertension. The final diagnosis was a metastatic tumor thrombus in the left main pulmonary artery, though histological confirmation was obtained only at autopsy. A few cases with several subcutaneous metastases have been reported. Quite a number are acral, in the fingers, particularly the thumb (Froimson).
A few cases with lymph node metasases have also been reported (Matsumoto et al.).

We found some reports on oral metastases. In all patients several other metastases were present as well, and the presentation was the first sign of metastatic disease (Table 14.69).

Table 14.69 - Chondrosarcoma
Metastases in the Oral Cavity Reported

Author	Pat	Primary	Site of Metastasis
Goldstein 1943	M10	Tibia	Mandible
Kemper1944	F13	Tibia	Maxilla
Robinson1947	M11	Tibia	Mandible
Hardman1949	F41	Femur	Mand+Max.
Roser1976	F31	Scapula	Maxilla(‘)
Englert 1978	M43	Foot (EO)	Mandible(“)
Sherr 1985	F47	Hip	Maxilla (°)
Taicher 1991	F45	Calf(EO)	Maxilla

(‘) vulva, thumb, toe, scalp, skull, knee, ankle;
(“) calf, popliteal fossa, inguin.nodes; (°) brain;
EO: extra-osseous.

Other uncommon metastatic sites have been reported. Two years after diagnosis of a CS at the ‘right hip’ a M36 presented with distal phalangeal metastasis at the ring finger of both hands (Lambert et al.). Another patient (M30) had a subcutaneous metastasis in the left little finger, three years after resection of a tibial chondrosarcoma (Bansal et al.).
Three years after amputation for a CS at the calcaneum, a M79 presented with hoarseness. A solid tumor in the thyroid was found to be solitary metastasis of the chondrosarcoma, though a few months later overt pulmonary metastases were observed (Bakx et al.).
An unusual case has been reported by Schenk et al. They had to do an emergency removal of a tumoral tissue plug that was liberated at bronchoscopy from an endobronchial metastasis due to a pelvic chondrosarcoma.

Intussusception was the result of a large jejunual metastasis from a chondrosarcoma of the right humerus operated 3 years earlier (M64) (Kehoe et al.).

Chondroblastoma

In the cases labeled as benign chondroblastoma, some have reported with distant metastases. Revie-wing the pathology and the reported cases, Kunze et al. could retrieve 7 cases. There were multiple lung metastases in all cases and in one, there was involvement of liver and diaphragm. Since then several new cases have been reported (Khalili et al.).

METASTASES from EWING's SARCOMA

Ewing's sarcoma is a primary, small round-cell tumor of the bone, most frequently occurring in children and adolescents.
Distant metastases occur frequently and are primarily in the lungs and other bones, but they have been described as occurring in several other locations as well.

In spite of the relatively high number of patients treated in international protocols, precise data on the incidence of spread as well as pathological aspects are absent in the literature. We have scanned hundreds of 'trial' reports and treated series, but were unable to find adequate data on the site and number of metastases. Metastatic spread is wide and indiscriminate, invol-ving almost every site. Lymphatic spread is relatively common but usually overshadowed in the clinical presentation by the symptomatology of the pulmonary or skeletal metastases.
The only adequate and well-studied data has been reported in 1975 from a series of 47 patients registered at the Bristol Bone Tumor Register. The first aspect examined was the time of presentation, a rarely addressed feature in oncology (fig. 14.12). It would appear that the initial metastasis in patients with long bone tumors are evenly spread between pulmonary and extra-pulmonary sites.When other bones are involved as primaries, there is apparently a propensity for extra-pulmonary sites, at least in the early phase.
The same authors also studied the site of metastases at inital presentation and at death (fig.4.13). The pattern of spread did not depend on the site of the primary, although a relatively increase of the number of vertebral metastases occurs when the primary is not in the long bones, probably by Batson's pathway. Tumors in the long bones apparently lead to more pulmonary metastases.

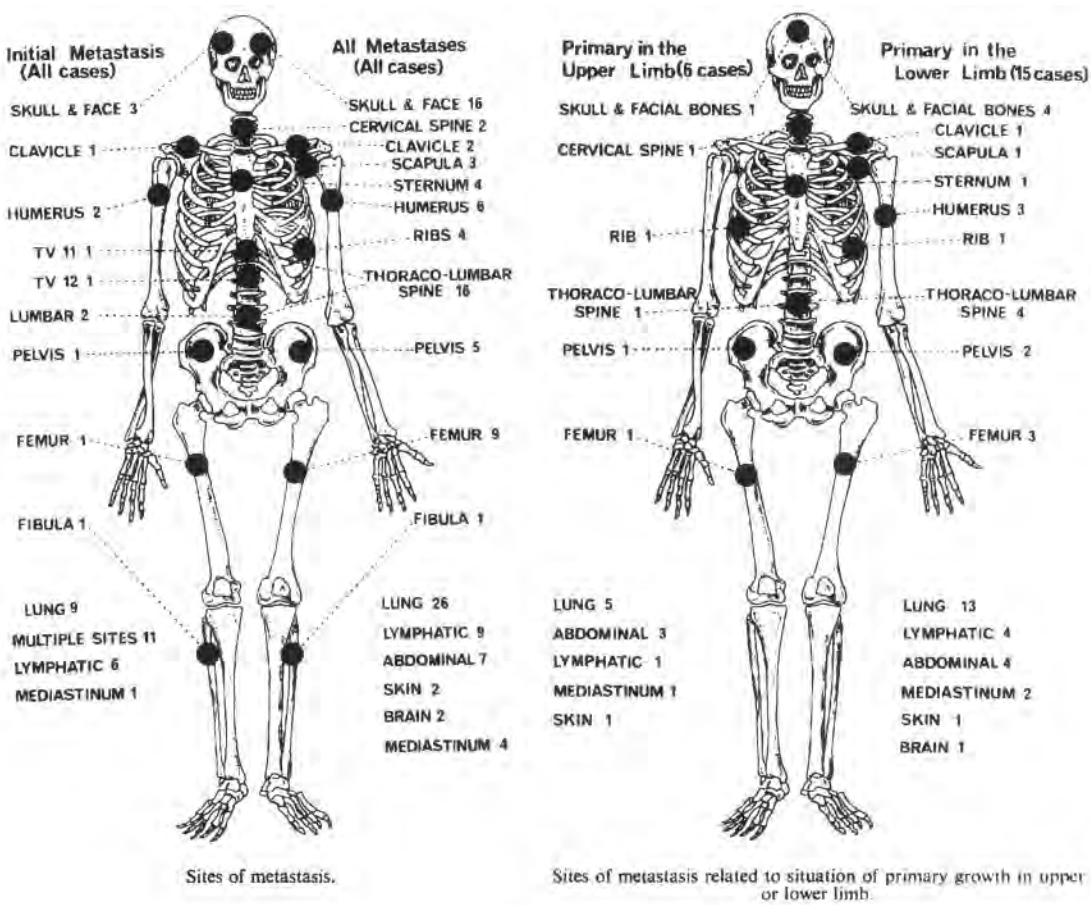

Fig. 14.12 - Ewing's sarcoma - Left: Site of metastases; Right: Site of metastases related to the location of the primary growth in the upper or lower limb (from MacIntosh et al., with permission)

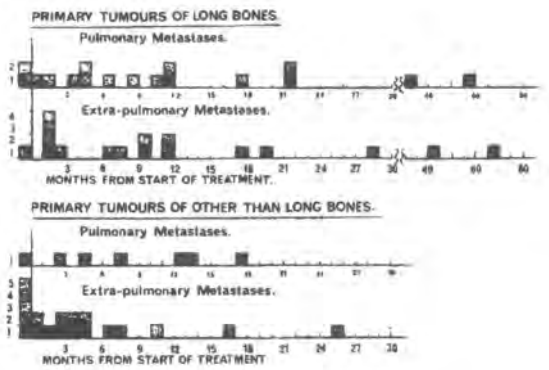

Fig.14.13 - Timely spread of distant metastases in 47 patients with Ewing's sarcoma (MacIntosh et al., with permission)

Hayes et at. have reported on 65 patients. Metastases were found at diagnosis in 18 (27%). The metastases were in the lungs in 7, in another bone in 8, in the bone marrow in 3 and in the pleura in 3. One patient had a metastatic lymph node. The occurrence of metastases during the follow-up was not reported.

Of 27 consecutive patients, 15 developed evidence of CNS metastases in the series reported by Mehta et al. Data on site within the brain were not given. Another series of 12 patients with CNS metastases was reported by Colak et al., but it mainly concerned spinal cord compression and in 3, mention is made of a brain metastasis.

Reviewing the records of 445 patients, Trigg et al. noted a CNS involvement in 10/445 or 2.2%. Cortical mass lesions were observed in 8/445 (1.8%) patients and meningeal involvement in 2/445 or 0.4%. All brain involvement occurred during follow-up. In almost all patients, the CNS involvement was associated with other metastases. Meningeal or intraparenchymal CNS was the initial site of recurrence site in 3 of the ten patients.

A few other 'out-of-the-ordinary' cases have been reported. In all patients pulmonary and other bone metastases were also present (table 14.70). We also know of a reference on placental metastases, but the report was not available.

Table 14.70 - Ewing's sarcoma
Distant Metastases 'Out-of-the-Ordinary'

Author	Pat	Primary	Site of M	Interval
Greenberg '82	F19	Le.Tibia	Placenta(°)	4 yrs
Rubin 1985	M28	Pubic bone	Pancreas	2 yrs
Green 1986	F1	Scapula	Lung Retina	2 yrs
Sturmberg '88	F4	Ri.pelvis	Caval thrombus(')	2 yrs
Zachariades '89	M7	Le.leg	Ri.Mandible	1 yr
Janssen '94	F20	Os Temporale	Heart LeV.	8 yrs
Mulligan'97	M26	Femur	Pancreas	Simult
Gunduz '97	F19	Femur	Bone-Lung-Iris	8 mo

(°) among several other metastases
(') Tumor thrombus extending from inferior vena cava to the tricuspid valve

A patient (F15) presented 3 years after first treatment for an extra-osseous Ewing's sarcoma of the thoracal cavity with jaundice. It was caused by a metastasis in the pancreatic head (Obuz et al.).

Althoughnot likely to affect treatment outcome, data relating to metastases should be available in the data-files of the various trial. Analysis of the data would assist charting of the metastatic pattern.

METASTASES from CHORDOMA

Chordomas are lobulated neoplasms composed of physaliphorous cells and their precursors. Some have atypical, epithelioid or spindle cell features. Fewer than 15% arise in the mobile spine, with 48% in the sacrococcygeal region and 40% in the spheno-occipital skull base.

> Virchow has described jelly-like nodules on the inner surface of the base of the skull. Believing they were cartilaginous growths, he called them ecchondroses physaliphora, derived from the greek for sail or basket, referring to the histological appearance of the cells. They are notochordal remnants.

It is not known wether they are likely to give rise to metastases. The published series gives scant attention to this, paying more attention to the results of the applied treatment.

Fagundes et al. mention a rate of 6.3% in 204 irradiated patients, while Sundaresan et al. quote a rate of 60% in their 18 vertebral and 27% in the 36 sacral chordomas, a significant difference not quoted in any other report. The latter was probably a series biased by referral. Volpé et al. show a rate of 20% in their 25 spinal chordomas.

Table 14.71 - Chordoma
Distant Metastases reported
Literature Review by Chambers et al. 1979

Lungs	40	Heart	5
Lymph nodes	23	Subcutaneous	4
Liver	15	Adrenal	3
Bone	12	Skin	4
Muscle	6	Peritoneum	2
Pleura	5	Generalized	4
Brain	5	Other(')	6

(') omentum, bladder, pancreas, mesentery, pericardium, meninges

On the other hand Bjornsson et al. admit only 2 patients with metastases in their series of 40 patients (5%) at the mobile spine. It is probable that the easier accessibility of these sites allows a more adequate surgery. Reviewing the literature in 1979, Chambers et al. retrieved 70 cases reported to have metastases. The various different sites are in table 14.71.

The main metastatic site is the lung, followed by liver and other parts of the skeleton. Sibley et al. reviewed the literature of metastatic chordoma in children and

could retrieve 16 cases in 1987. There is apparently some relationship between the site of the primary and the site of the metastases, as the 7 located at the sacroccocygeal region only had infra-diaphragmatic metastases excluding the lung site (table 14.72). The intrabdominal dissemination is most probably via the different venous plexus.

Table 14.72 - Chordoma in Children (0-19yrs)
Site of Metastases (N=16)
Literature Review by Sibley et al. 1987

	Clivus to T12	SacroCoccyx
Lung	8/9	4/7
Bone	1	--
Skin	1	--
Heart	1	--
Cervical node	1	--
Heart	1	--
Soft tissue	2	--
Liver	--	2
Inguinal nodes	--	3
Urinary Bladder	--	1
Adrenal	--	1

Metastases in the Central Nervous System

As with tumors of the central nervous system, we found 4 cases of intradural spread, apart from other metastatic involvement (Table 14.73).

Table 14.73 - Chordoma
Metastases to the Intradural Space
Case reports

Author	Pat	Tum.	Site of M	Interval
Fox 1968	F58	Sa Co	T6-Cauda Eq.	5 yrs
Fox 1968	F67	Thor	T11-L1	45 mo
Krol 1989	M59	Sa Co	Lumb.Multiple	6 yrs
Krol 1989	M41	Cliva	L2-Cauda Eq.	2 yrs
Fagundes'95	??	Cerv(?)	T12	??

Table 14.74 - Chordoma Metastatic to the Brain
Case reports

Author	Pat	Tum.	Site of M	Interval
Morris1947	F27	SaCo	Le.Frontal	18 mo
Higinbotham'67	??	SaCo	??	??
Fox 1968	F58	SaCo	Ri.Parietal	5 yrs
Fichard 1974	M41	SaCo	Pituitary	2 mo
Chambers '79	M59	SaCo	Brain	??
Hall 1995	M29	SaCo	Le. Occip.	3 yrs

All reported cases also had pulmonary and some other metastases. A case described by Fox et al. had metastasis to the sternum, periaortic nodes and the parietal lobe of the brain. The pathway is most probably detachment of cells within the spinal canal. Some rare metastasis to the brain have been reported. All were from a sacrococcygeal chordoma (table 14.74).

Metastases to the Skin 'Chordoma Cutis'

Cutaneous metastases have been reported in several cases (table 14.75). According to Chambers et al., it occurs in 5% of all patients with chordoma. A review the several reports on cutaneous involvement show that many must be considered regional spread from the surgical incisional or subcutaneous lymphatic spread. In the series of Su et al., only 1 of the 19 cases is a true distant metastasis, one with a scalp metastasis from a sacral chordoma. Gagné et al. reporting on 16 cases admit that 13 had local recurrences and only 3 could be considered asdirect cutaneous extension.

Table 14.75 - Chordoma Metastatic to the Skin
Case reports

Author	Pat	Tum.	Site of M	Interval
Malone 1987	M65	Lumb	Eyelid(")	3 yrs
Peramezza '93	M61	SaCo	Multiple(')	6 mo
Su 1993	F62	Sacral	Scalp	5 yrs
Jones 1994	M67	Sacral	Scalp	7 yrs
Ogi 1995	F22	Clivus	Thigh	1 yr
Cesinaro '95	M40	SaCo	Nose	16 mo
Couldwell'96	F8	Clivus	Incision Site	2 yrs

(") single lesion
(') shoulders, left arm, face, head

In two cases reported by Chambers et al. the skin lesion occurred before the primary became evident. Reviewing the literature, Couldwell et al. found that all metastases to the skin occurred only in the sacral, scalp, face or neck region. Their case was the sole one at the thoracic site, and within the surgical incision site. The case of Peramezza et al. does not fit within this delineation.

Metastases to the Mandible

A peculiar solitary metastasic site even from a sacral chordoma, is the mandible. We found three reports on the subject (table 14.76). They all concerned a female patient, the metastasis was in the right mandible in all and the interval to the metastasis was 3 years.

Table 14.76 - Chordoma Metastatic to the Mandible

Author	Patient	Primary	Side	Interval
Gorsky 1983	F64	Sacral	Ri	3 yrs
Woolf 1984	F64	Sacro Cocc.	Ri	3 yrs
Slee 1989	F32	Sacro Cocc	Ri	3 yrs

Other Metastatic Sites

As is usual with the rare tumors, the metastatic cases generally have more attention and been given rise to more publications. In the case of Wang et al., an axillary node metastasis was noted as first recurrence after surgery for a sacrococcygeal chordoma, probably by subcutaneous spread. Later, several cutaneous nodules were observed and at autopsy, metastases at the heart, retroperitoneum, liver and several muscular and subcutaneous sites.

An F78 presented with a mass in the nasopharynx and

multiple cervical nodes, a clinical presentation common for a nasopharyngeal cancer, but at histology it turned out both to be chordoma (Singh et al.).

Three and a half years after resection of a sacral chordoma, a F45 presented with a clear ovarian mass, laparotomy showed it to be a solitary ovarian metastasis from the chordoma (Zuckerberg et al.).

Three years after palliative treatment for an extensive sacral chordoma, cutaneous metastases appeared in a M57, with progressive deterioration. At autopsy, the skin of the whole lower half of the body was found to be full of cutaneous nodules and pelvic and para-aortic metastatic lymph nodes as well. Multiples nodules were visible all over the heart, in several muscles, but not in the lungs (Yarom et al.).

Recently, Fischbein et al. reported on a M49 presenting with hoarseness six months after surgery for a chordoma at the coocyx. The metastasis was in the laryngeal cartilage.

Four years after resection of a sacral chordoma, a F64 presented with exertion dyspnea complicated with edema of the neck and face and of the lower extremities. Echocardiography revealed a massive pericardial effusion and a tumor in the free wall of the right ventricle. Surgery confirmed metastatic chordoma (Oda et al.).

The following other cases also deserve some attention. Four years after surgery for a sacrococcygeal chordoma, a M58 presented with a nodule on the glans penis. It turned out to be a metastasis (Saltzman et al.). The case just mentioned also developed peritoneal metastases after placement of a ventriculo-peritoneal shunt for relief of a hydrocephalus.

In two cases both involving boys with intra-cranial chordoma, pulmonary metastases and early death attributed to pulmonary tumor emboli occurred (Auger et al.). In another case, a 17 month old boy, the child was reported to have died of multiple pulmonary metastatic emboli, from a clival chordoma (Brooks et al.).
A presacral mass was observed in a 3.5 year old boy and turned out to be an extraskeletal chordoma. It soon metastasized within the peritoneal cavity and lungs (Hordton et al.).

METASTASES from ADAMANTINOMA

Adamantinoma is a rare bone tumor. In the period up to 1994, only 200 cases had been reported in the literature. Twenty percent will develop metastases (Lokich). The most frequent involved sites are the lungs, with multiple nodules. Almost all case reports concern the occurrence of pulmonary metastases. The interval can be as long as 16 years (Cohn et al.).

Beppo et al. have reported on a case with a rib primary metastasizing to the liver. They cite two cases from a review on abdominal metastases, and an inguinal node in 3 and to another bone in two.

METASTASES from DENTAL TUMORS

Dental tumors exhibit a very wide spectrum of different histologies. Malignant epithelial odontogenic tumors are very rare. They may arise from the epithelial components of the odontogenic apparatus. The rests of Malassez, the reduced enamel epithelium surrounding the crown of an impacted tooth, the rests of Serrs in the gingiva and the linings of odontogenic cysts represent the precursor cells for malignant transformation.
Odontogenic carcinomas include malignant ameloblastoma, ameloblastic carcinoma, primary intra-osseous squamous cell carcinoma, clear cell odontogenic carcinoma and malignant epithelial ghost-cell tumor.

Because metastatic carcinoma is the most common malignancy of the jaws, the diagnosis of a primary intra-osseous carcinoma must always be made by exclusion of any metastatic disease. It is also important to differentiate clear-cell odontogenic carcinoma from renal cell metastases, what can be done by immunohistochemical means (Eversole).

Ameloblastoma

Of the jaw tumors, ameloblastoma accounts for only 1%. About 85% are in the mandible and the other 15% in the maxilla. Local recurrence is the major problem, an expression of the local malignancy of a so-called benign tumor. Distant metastases are rare and occur mainly in the lungs. Most cases have been reported after a delay of more than 10 years after initial treatment.
Up to 1999, 41 cases were reported in the English-language literature. In 8 cases, it originated from a maxillary primary. The lung metastases were solitary in 5, but can be present at first diagnosis. In all others, when reported, there were multiple metastases (Henderson et al.).

The other sites were principally lymph nodes including cervical, submandibulary and mediastino-hilar nodes. More distant sites were the pleura, diaphragm, brain, temporale bone, liver, kidney and small intestine. The median interval between diagnosis of primary and the metastases was 11.1 years, with a range of 2 to 31 years (Kunze et al.).

Other Dental Tumors

We are aware of two reports on metastasizing clear cell odontogenic carcinoma.
Milles reported on a case metastasizing to lymph nodes. Reviewing the literature, they could retrieve 3

other cases with lymph node metastases, but also one with pulmonary metastases. The case reported by Kao et al. metastasized to the axillary skin, the brain and the lungs.

METASTASES from EXTRA-RENAL WILMS' TUMOR

An extrarenal Wilms' tumor is extremely rare. It will usually be located along the renal-gonad line. We are aware of only one reported case with distant metastases.

Diagnosis of an extrarenal Wilms' tumor was made at the age of 2 (F2). A cystic mass was observed in the posterior compartment of the subarachnoid space displacing anteriorly and significantly compressing the two hemicords and their reunited single cord or diastematomyelia. A well-encapsulated spheric nodule was encountered and opened in the canal. At histology the diagnosis of Wilms' tumor was made. Two years later a mass in the left cerebellar hemisphere was seen at CT (Mirkin et al.).

METASTASES from SOFT TISSUE SARCOMA

Soft tissue sarcomas are a group of tumors with a rare large diversity of histologies, depending on the cell of origin. As far as tumor cell spread is concerned, they have all a similar pattern, with a majority of pulmonary parenchymal metastases and a 'secondary' widespread possibility in various organs. Pattern studies are rare.

There have been almost no reports on the autopsy metastatic pattern. Vezeridis et al. have reported on the type of recurrence after initial treatment, under the title 'metastatic pattern', although they only examined the tendency in 9 sites, withoutproviding detailed data. The most frequent first recurrence site was local in 47.5% of the 'recurrent' patients, followed by the lung in 38.0%. Of the 242 patients, 33 had two-organ recurrence and seven a 'three-organ' recurrence. The lung was the most frequently involved site from the third recurrence on, while a progressive increase of bone and brain involvement was noted. The progressive involvement of the peritoneum is striking, but the study did not examine wether there was any association with the primary site neither its histology.

DelaMonte et al. have studied the metastatic pattern of 22 subjects who died of a rhabdomyosarcoma and observed that those patients with the embryonal type had twice as many metastatic sites as the alveolar type at least at some sites, and excluding the liver, but in general, no particular difference was observed (table 14.77).

Reviewing 118 cases of leiomyosarcomas of various origins, MacLeod et al. listed the distant metastases as reported (table 14.78).

Table 14. 77 - Rhabdomyosarcoma
Distribution of Metastases at Autopsy (N=14)
Data of DelaMonte et al.

Histology Type:	Embryonal	Alveolar
Regional	N=14	N=8
Head	29%	13%
CNS	21	13
Neck	36	38
Thorax	64	50
Abdomen	71	50
Pelvis	57	13
Extremities	29	25
Organ/Tissue		
Soft Tissues	79	63
Serosal surfaces	71	50
Lymph Nodes	64	63
Lungs	57	50
Bone Marrow	57	38
Endocrine organs	29	25
Liver	14	25

Table 14.78 - Soft Tissue Sarcoma
Leiomyosarcoma - Distant Metastases (N=118)
From Data of MacLeod et al.

Liver (total)	37.2%	Lung	16.9%
Liver (necrotic)	24.5	Soft-tissue	7.6
Ascites	6.7	Bone	3.3
Retroperitoneal	10.1	Spleen	(1)

Reporting on two patients with metastases to the breast from a previously treated rhabdomyosarcoma, Santos-Miranda et al. reviewed the literature and could retrieve 56 other reports on this particular metastases from RMS. Bilaterality was noted in 12 patients. They noted a median age of 15 years in these patients and an interval of between 16 and 19 months before the diagnosis of the metastasis.

Reporting on 104 patients with synovial sarcoma treated by the Scandinavian Sarcoma Group, Skytting mentions metastases occurring in 34. The metastases appeared first in the lungs in 28 and in the lymph nodes or multiple other sites in six. The median interval to metastases was 1.5 (0.2-6) years.

Recent data concerning the rare form of alveolar soft part sarcoma were made available in a report by Portera et al. Sixty five percent of the 70 cases were already metastatic at presentation, white a 91% lung involvement and 18.7% at the brain was found. The small number does not permit to discern any pattern.

Lymph Node Metastases

It is commonly believed that soft-tissue sarcomas (STS) only metastasize along the vascular system and not the lymphatic system. While this event is indeed

rare and hardly mentioned in the small patient series reported, an extensive literature reviews has been published by Mazeron et al. (table 14.79).
Later, Fong et al. identified 46 or 2.6% patients with lymph node metastases in a series of 1,772 patients treated at one institute. They observed a clear difference in incidence depending on histology (table 14.79), but also according to the primary site (table 14.80).

Table 14. 79 - Soft Tissue Sarcoma
Incidence of Lymph node Metastases
Influence of Histology

	Mazeron 1987 N= 5,257(‘)	Fong 1993 N=1,772 (°)
Histology		
Fibrosarcoma	25.1%	0.0%
Mal.Fibr.Hist.	10.2	2.5
Rhabdomyosarcoma	14.8	2.8
Leiomyosarcoma	4.0	4.0
Angiosarcoma	11.4	13.5
Synovial Sarcoma	13.7	1.3
Epithelioid Sarcoma	2.0	16.6
Liposarcoma	3.1	0.7
Alv.Soft part Sarcoma	12.5	0.0
All histologies	10.7	2.6

(‘) Literature Review
(°) Patients from one institution

Table 14.80 - Soft Tissue Sarcoma
Lymph node Metastases and Anatomic Site of Primary
Data of Fong et al.

Head and Neck	10.9%
Upper Extremity	15.2
Trunk	10.9
Thoracic	0.0
Visceral	6.5
Other	15.2
Lower Extremity	41.3

The data show the high incidence for angiosarcomas and epithelioid sarcomas. Patients treated before 1987 as described in the literature were certainly not treated according to modern standards of surgery, implicating a higher risk to metastatic spread. The patients reported by Fong were from the Memorial Hospital (New York) and treated according to a more standardized oncological protocol, and probably resulting in a lower degree of metastatic spread.
The higher incidence of lymph node metastases for the primaries at the lower extremity is surprising indeed .
Reviewing 183 adults wth STS, Gaakeer et al. found that 15 or 8.2% developed lymph node metastases. There was a variation according to histology,though the numbers in each histological category were relatively small. It was noted in 10% of the MFH, 11% in the leiomyosarcomas and 20% in the group comprising 9 synoviosarcomas, 8 clear-cell sarcomas and 7 epithelioid sarcomas.
Reporting on a case of primary leiomyosarcoma of the maxilla with regional lymph node metastasis, Izumi et al. reviewed the literature on oral leiomyosarcoma and found an reported incidence of regional lymph nodes in 23% in the 60 patients.
Recently Lev-Chelouche et al. reported on 10 patients with various different STS of the lower extremity and metastasizing to the retroperitoneal nodes. Four were liposarcoma, three were MFH and one each of schwannoma, synovial sarcoma and leiomyosarcoma. The metastases were observed between 6 and 120 months, with a mean of 45 months. Symptomatology was vague or absent. In six patients the retroperitoneal mass was the first site of recurrence.

Metastases to the Lungs

The incidence of pulmonary metastases in the lung is high. As is usual in the oncological literature, little attention has been paid to the pathologic and demographical features of this metastatic site in STS. Such data are almost absent, even in the various different reported series on surgical resection of metastases. We have found a few data, certainly biased by their selection for surgery. Ueda et al. have provided data on 23 patients (table 14.81). From their data, we can conclude - as already known, in fact - that most patients have a large number of metastases and with a rather large size, according to the cannon-ball pattern.
Billingsley et al. have reported on the incidence of pulmonary metastases according to the primary site (table 14.82), based on a series of 3,149 patients.

Table 14.81 - Soft Tissue Sarcoma
Some Features of Pulmonary Metastases (N=23)
Data of Ueda et al.

Number	<6	4
	>5	19
Laterality	Unilateral	2
	Bilateral	21
Maximal Size	<6cm	13
	>5cm	10
Localisation	subpleural	9
	Extrapleural	12

Table 14.82 - Soft Tissue Sarcoma
Pulmonary Metastases according to Primary Site
Modified from Billingsley et al. (N=3,149)

Head and Neck		18%
Extremity Trunk		26
Thoracic		23
Retroperitoneal		14
GastroIntestinal		6
Gynecologic		38
Genito-Urinary		23
Skin - others		36
	Overall	22.8%

If the data are analyzed as the percentage of all pulmonary metastases, the extremity-trunk groups account for 65% of all metastases, due to the fact that they account for 58% of all tumors.

One particular type of pulmonary metastases is the

endobronchial form. Udelsman et al. have reported on 4 patients and retrieved 8 other reported cases from the literature. Three were from a uterine leiomyosarcoma and the other were from various histologies. An unusual case has been reported by Schenk et al. They had to remove in emergency a tumoral tissue plug that was detached at bronchoscopy from an endobronchial metastasis from a pelvic chondrosarcoma.
Pulmonary embols from metastatic osteosarcoma have also been reported. They can be visualized at bone radionuclide scintigraphy (Hoefnagel et al.).

Metastases to the Brain

Although not the most frequently involved site, brain metastases has received most of the attention. A number of reviews and raelatively large series have been reported, mixing however osteogenic and STS. A collation of the data of the four most recent series totalling 53 STS patients (Table 14.83), shows that 37% of the metastases are located at the frontal lobe and 22% at the parietal. If the 5 parietofrontal are added, this makes 47% or nearly half at the frontal lobe.
Haykal et al. have reported two cases of leiomyosarcoma metastatic to the brain, without mentioning the primary site. Liwnicz et al. have reported on a mixed malignant mesenchymoma of the thoracic wall in a M84, metastatic to the brain stem.

Table 14.83 - Soft Tissue Sarcomas
Site of Brain Metastases in 4 reported series(')

Parietal	12	ParietoOccip.	3
Occipital	3	Parieto-Frontal	5
Frontal	20	Multiple	5
Temporal	7		
Cerebellum	1		

(') series of Bindal et al.13 pat.; Wronski et al., 16 pat. Salvati et al.,9 pat., Ogose et al., 15 patients.

Reviewing the cases at their hospital, Bryant et al. found 12 cases of brain metastases in a series of 744 STS or 1.6%. They remarked a proportionally higher rate in the group of alveolar soft part sarcomas (ASPS), but the site of the metastases within the brain was not reported.
Lillehei et al. have reported on a patient with ASPS presenting with a single brain (occipital) metastasis 33 years after first treatment. The interval was 'only' 26 years in a patient treated for a liposarcoma of the right lower extremity metastatic to the right temporal lobe (Arepally et al.).

A meningeal metastasis from a mandibular leiomyosarcoma was reported in a M70, 5 years after first treatment (Buff et al.).

Metastases to the Heart

Earlier reports mention cardiac metastases only at autopsy. Present-day imaging methods allow the alert oncologist to diagnose cardiac involvement premortem.
While a few case reports are at hand, the ad-hoc study of Hallahan et al. is the only one shedding light on the problem. In a consecutive autopsy series on 120 STS-patients, they detected cardiac metastases in 30 or 25% of the patients, of whom half had myocardial metastases, one-third pericardial involvement and both in the rest. There is not much difference according to the histology type, nor according to the primary site, except the relatively high number of involvement in primary pulmonary and/or mediastinal sarcomas, which may be explained by contiguity (table 14.84).

Table 14.84 - Soft Tissue Sarcoma
Cardiac Metastases - Pathology Features
Data of Hallahan et al.

Histology			Site	
Uter.LeiomyoS.	4/12	33%	Visceral	26%
GIT leiomyoS.	4/10	40	Extrem.Trunk	22%
MFH	4/12	33	Lung-Mediast	71%
Child-Rhabdo.	7/16	44	Retroperit.	22%
NeurofibroS	3/10	30	Head-Brain	11%
Undifferent. S.	2/5	40		
Kaposi	2/6	33	Myocardium	15/30
Fibrosarcoma	1/9	11	Pericardium	10/30
Synovial Sarcoma	1/5	20	Both	5/30
Other	2/35	6		
Total	30/120	25		

The most common cardiac finding was chronic heart failure, occurring in 10 of the 24 evaluable patients. Echocardiography is very valuable though it only was applied in most of the recent patients.

A F22 presented one year after surgery for a RMS at the calf with extreme dyspnea. At autopsy several cardiac metastases were found, associated with a lot of other metastases elsewhere (Sherman et al.).
Recently, a case (M62) was reported by Lopez et al., operated previously for a colonic leiomyosarcoma. He presented 6 years later with dyspnea and general weakness. Several imaging studies showed embolic events probably derived from a large left atrial mass extending to the mitral valve. The mass was evacuated at surgery and was friable. At pathology, tumor with thrombi was found. Another mass was seen at surgery at the visceral pleura. This was resected later and confirmed to be metastatic leiomyosarcoma.

Metastases to the Liver

Hepatic metastases would appear to be relatively uncommon in STS. Only a few authors have addressed this site specifically.
Jaques et al. identified 65 patients in a series of 981 adult patients, or 6.6%. In 55, or 85% of these patients histology was a leiomyosarcoma. The metastasis was present at first diagnosis in 13, or 20% of the patients. The primary was located in the abdomen in 94% of them, visceral in 35 and retroperitoneal in

24. The prevalence according to site is on table 14.85. Other authors reported on hepatic metastases quoting an incidence value without further anatomical or pathological data. So Haffner et al. quoted an incidence of 1.3%.

Another data set was published by Lang et al. on 26 patients with a leiomyosarcoma and liver metastases (table 14.86).
The radiological aspects of 10 metastases visible at T1W-MRI have been described by Soyer. Nine were homogenous and one contained areas of necrosis. Of the 16 seen at TW2-MRI, 12 were well delineated and completely homogenous, comparable to the benign hemangioma of the liver.

Table 14.85 - Soft Tissue Sarcoma
Hepatic Metastases according to primary Site (N=981)
Data of Jaques et al.

Abdomen	22%
Retroperitoneum	16%
Viscera	62%
Gynecology	2%
Genito Urinary	5%
Thoracic	7%
Lower Extremity	0.8%
Alll other sites	0.0%

Table 14.86 - Soft Tissue Sarcoma - Leiomyosarcoma
Pathology of Liver Metastases(') (N=23)
Data of Lang et al. (2000)

Unilobular		66%
Bilobular		33%
Number	1	44%
	2	13
	3	17
	More than 3	26%
Diameter of largest		8cm (2-25)
Other metastases present in		43%

Metastases to Bone

While all reviews mention skeletal metastases, only Yoshikawa et al. have provided adequate distribution data. After treating 277 patients with STS, they observed skeletal metastases in 28, or 10.1%, within a period of 18.6 months after admission. Four patients had metastases at admission. Patients with alveolar soft-part sarcomas, dedifferentiated liposarcoma, angiosarcoma and rhabdomyosarcoma tended to have the highest incidence (table 14.87).
Reporting on a series of 109 patients, Jager et al. observed bone metastases in 7%, at least as frequent as lung metastases. No particular pattern was observed. In 3 patients, the bone metastases were solitary, without any other site being involved.

The metastases were axial in 64%. The statistically significant difference between the number observed in the ipsilateral bones and the contralateral ($p<0.01$) is striking. In the first group, the metastases were regional in 13/19. The data reported in table 14.88 shows that all contralateral metastases came from a right-sided tumor; five from the lower and one from an upper extremity sarcoma. More data need to be reported to confirm this particular pattern, most probably ascribable to the plexus of Batson.

Table 14.87 - Soft Tissue Sarcoma
Bone Metastases according to Histology(')
Modified from data of Yoshikawa et al.

	N	Percent with
MFH	74	8.1%
Liposarcoma	49	4.1
Synovial Sarcoma	40	7.5
Mal.Schwannoma	28	10.7
Rhabdomyosarcoma	15	26.7
Leiomyosarcoma	13	7.7
Alveolar Soft Part Sarc.	9	55.6
Angiosarcoma	4	50.0
Unclassified	14	14.3

(') no skeletal metastases observed in the other types

Another report on skeletal metastases has been published by Wong et al. Reviewing the records of 227 patients, they observed 46 (20.2%) patients with bone metastases (table 14.89). The mean or minimal follow-up time was not stated. The mean interval was 2.7years (range 2mo - 15.6years). The incidence according to histology was not reported. Metastases were observed in 65 sites, with 72% axial. Of the vertebral lesions, the metastases were in the body in 56%, 33% the appendages and 11% in both. The rib and the femur each had 18.5% of the metastases.

Table 14.88 - Soft Tissue Sarcomas
Features of Bone Metastases observed
From data of Yoshikawa et al.

Axial Sites		'Lateral' Sites	
Skull+ Mandible	5	Scapula	3
Cervical Spine	5	Humerus	2
Thorac.spine (1-6)	5	Ribs	4
Thorac.spine (7-12)	7	Ilium	7
Lumbar-Sacrum	6	Femur	9
		Tibia	3
		Foot	3

Metastatic Sites	Ipilateral	26
	Contralateral	6
	Axial	27+(')

(') in two patients multiple.

Table 14.89 - Soft Tissue Sarcomas
Site of Bone Metastases observed
Modified from data of Wong et al.

Skull	7	Humerus	3
Cervical Spine	3	Lumbar Spine	9
Scapula	3	Pelvis	8
Sternum	1	Sacrum	3
Ribs	12	Femur	12
Thoracic Spine	4	Total	65

The radiology of the bone metastases was osteolytic

in 88% and osteoblastic in 12%. The majority (55%) had a moth-eaten pattern, while a 'geographic' pattern was seen in 29% and a permeative pattern in 12%. Radionuclide scan was not as sensitive in the visualization asit is for other neoplasms.

Metastases to the Oral Cavity

The oral cavity site is not an uncommon one and various case reports have been published. Sengun et al. retrieved 53 cases of malignant hemangioendothelioma of 'the oral cavity', but it is not clear if it concerned primary or secondary cases (table 14.90).

Table 14.90 - Soft Tissue Sarcoma
Metastases to the Oral Cavity
Case Reports

Author	Pat.	Primary	Site of M	Interv
Brook 1980	M61	Omental AS	Mand.Maxill	Simult
VanHale 1981	F47	L.Extr.MFH	Gingiva Sup.	4 yrs
Toth 1981	M64	Tibia A.S.	Gingiva inf.	2 mo
Sengun 1986	M16	Ankle H.E.	Mandible	3 yrs
Epstein 1987	F38	Breast AS	Gingiva(mult)	2 yrs
Porter 1988	M25	M.Brachialis	(APS) Tongue	3 yrs
Geist 1990	M60	Rib MFH	Tongue	14 mo
Bogart 1990	F58	Pulm.Leio	Gingiva Sup(°)	2 yrs
Karr 1991	F41	Le.calf Syn.	Mandible	6 mo
Karr 1991	F63	Le.Foot Syn.	Mandible	21 mo
Poulopoulos'01	F61	Breast A.S.	Mandible	2 yrs

AS: angiosarcoma; HE: Malignant Hemangio-Endothelioma; APS: Alveolar Part Sarcoma; Syn.: synovio-sarcoma)
(°) also brain, cerebellum, soft tissue

Metastases to the Abdominal Cavity or/and GIT

Not much attention has been given to this site, although metastases seem to be common, according to autopsy data. They are probably more common than usually believed. Some case reports are in table 14.91.

Table 14.91 - Soft Tissue Sarcoma
Abdominal Metastases
Literature Cases Reported

Author	Pat.	Siteof Prim.	Metastases	Interv
Santoro 1992	M78	Buttock MFH	Colon(°)	1 yr
Shinagawa '92	M31	Le.Di.Femur MFH	Pancreas	2 yrs
Gorman 1993	F47	Thigh MFH	Ileum	6 mo
Konishi 1994	F34	Popliteal CS	Stomach	6 yrs
Zanarini '97	F23	Thigh Sarc	Peritoneum	1 yr
	M45	Thigh LS	Peritoneum	3 yrs
	M44	Popliteal LS	Peritoneum	4 yrs
Tranter 2000	F78	Upper arm MFH	Ileum(")	3 mo

(°) multiple irregular ulcer-like lesions
(") intussusception

Metastases to the Breast

Metastases to the breast were described as first manifestation of an 'unreported' large tumor in the left thigh in a F26. Histologically, it was an alveolar soft part sarcoma (Hanna et al.). Other patients with STS metastatic to the breast have been reported including a MFH of the buttock in a F41 (Rao et al.), and from a leiomyosarcoma of the foot in a F39 (Tulasi et al.).

Several cases have also been reported for rhabdomyosarcoma. Howarth et al. reported on 7 cases from a series of 108 consecutively treated rhabdomyosarcoma patients or 6.5%. There were even two male patients. In the 7 patients, the primary was located at the extremities, with only 22 patients having a pri-mary in these sites.

Reviewing the literature up to 1997, Hay et al. reported on 19 female patients from a total series of 1,399 female patients enrolled in the Intergroup Rhabdomyosarcoma Study (IRS). Metastasis to the breast occurred at the first diagnosis in 7, while it occurred in the follow-up solitary in 7 and with other metastases in 12. They retrieved 36 cases from the literature, and only 4 were a non-extremity primary. In two patients, the breast metastases was manifest before the primary, poning the difficult differential diagnosis with a primary RMS in the breast. The large size of the metastasis and the bilaterality occurring in about half of the patients is noteworthy. Only two male patients with breast metastases were retrieved, those described by Howarth cited above.

Other Metastases

Several case reports have illustrated the various sites that can be involved with distant metastases from soft-tissue sarcoma.

Multiple metastases were found at delivery in the placenta of a pregnant patient (F18) being treated for an orbital rhabdomyosarcoma, with widespread metastases. The infant was apparently tumor-free (D'Day et al.).

A paravaginal rhabdomyosarcoma metastatic to the orbit has been reported in a F20 by Fehrat et al.

Recently Simsir et al. reported on a M51 who presented eight months after surgery of a RMS (embryonal and alveolar type) of the left nasal cavity, with multiple facial cutaneous metastatic nodules.

Liposarcoma

Cheng et al. have stressed that in liposarcoma, distant metastases are extrapulmonary, in 13 of the 22 patients with metastases, even as in more than half extrapulmonary only. A soft-tissue site was involved in 7, bone in 3, liver and 2 and the rare site of thymus in 1. An intrarachidial metastasis from an unknown and barely palpable tumor in the right calf (liposarcoma) in a patient (M58) has been described by Kirollos et al.

An orbital metastasis from an abdominal (no further details) liposarcoma (F75), 4 years after initial treatment, was reported by Fezza et al., while an extensive metastasis to the skull and dura in a M44 6 years after

first treatment, was reported by Utsunomiya et al.

Leiomyosarcoma

A leiomyosarcoma of the small intestine presented initially as an umbilical tumor in a M40. Surgery disclosed multiple nodules all over the small and large intestine. The undersurface of the abdominal wall was also studded with multiple nodules (Powell et al.).

Gillner et al. have reported on a man (M71) with metastases to the scalp and thoracic wall presenting 9 months after resection of a leiomyosarcoma of the tunica vaginalis. Skin metastases are not un-ommon in leiomyosarcoma, as the authors retrieved 12 other cases from the literature. Among them, six had metastasized to the scalp and 3 to the breast. Eight were from primaries in the retroperitoneum and two shown to be from an uterine sarcoma.

A scalp tumor histologically shown to be leiomyosarcoma was the revealing sign of a large hepatic leiomyosarcoma in a F59 (Péquignot et al.).

A fatal pulmonary tumor embolism from a retroperitoneal rhabdomyosarcoma (M10) was reported by Soares et al.
A sarcomatous tumor of the kidney was the source of multiple peripheral arterial embolism in a 75-year-old man and was the first manifestation of the pimary (Liapis et al.).
A malignant axillary schwannoma was the source of an extensive tumor thrombus up to the right heart with a symptomatic vena cava superior syndrome in a girl (F15), associated with a significant degree of lymphedema of the arm (Ramanathan et al.).

METASTASES from GIT LEIOMYOSARCOMAS

Malignant sarcomas of the gastro-intestinal tract are rare tumors originating from the smooth musculature of the gut. They can occur from the mouth down to the anal canal.
The literature on the subject is made up of numerous case reports and small series buried in a large number of journals. Thanks to the diligent retrieval work and the dedication of the team of Dr.Skandalakis, there is now a very complete knowledge on the subject.

It is indeed much more appropriate to study these particular tumors according to their site of origin, as their progression and behavior depends to a large extent on the anatomical site. An esophageal leiomyosarcoma will behave differently from a colonic leiomyosarcoma.
We have taken the liberty summarizing the reports as far as metastatic behavior is concerned.

Oropharyngeal Leiomyosarcoma

Fifteen cases with metastases at diagnosis have been reported (Wertheimer-Hatch et al.). In ten, the lungs were involved and in nine there were lymph nodes. The other had metastases to the liver, the pleura, the subcutaneous tissue and a vertebra (each 1). One mimicked a meningioma. The risk of metastases increased with size (table 14.92). They must be differentiated from the not uncommon oral metastases from elsewhere.

Table 14. 92 - Oropharyngeal Leiomyosarcoma
Incidence of Metastases and Size
Review by Wertheimer-Hatch et al.

Size	N	N with metastases
<2 cm	13	0
2-5 cm	14	5 (35.7%)
>5 cm	5	4 (80.0%)

Esophageal Leiomyosarcoma

Hematogenous spread to the liver and lungs is common, but a large number spread through direct extension. In general, metastases occur in one-third of the cases.

Spread seems independent of the site (third) of the tumor. Size is not a good predictor, however, (table 14.93), nor does the pathologic aspect (infiltrative or polypoid). The liver is the most frequent site, followed by the lymph nodes and lungs.

Table 14. 93 - Esophageal Leiomyosarcoma
Distant Metastases according to location
Literature Review by Hatch et al.

Location	Metast.	Percent
Upper Third	4/20	20.0%
Middle-Third	10/33	30.3%
Middle+Lower Third	0/4	
Lower Third	19/48	39.6%
Lower Third and Stomach	2/7	28.6%
All	35/112	31.3%

Table 14.94 - Stomachal Leiomyosarcoma
Distant Metastases according to pathology
Literature Review by Davis et al.

Size				
<5 cm	13/37	35.1%		
5-9 cm	21/86	24.4%	Pathology	
10-14 cm	19/48	39.6%	Endog. 21/87	24.1%
>15 cm	35/69	50.7%	Exog. 57/154	37.0%
Multiple	5/23	21.7%	Intra-M 5/24	20.8%
			Dumb-bell11/18	61.1%
Location				
Cardia-Fund	17/43	39.5%		
Body	13/41	31.7%		
Antrum-Pylor	6/28	21.4		

Stomachal Leiomyosarcoma

Of the 283 cases reviewed, 33% had metastasized, with large tumors significantly in the majority. Tumors located both intra- and extramurally (dumb-bell) were more likely to metastasize than those with other growth patterns (Davis et al.) (table 14.94).
The most common site of metastases was the liver, followed by spread to the omentum or/and mesentery, lung and lymph nodes. Multiple metastases were observed in 22.8% of the cases with metastases.

Intestinal Leiomyosarcoma

These tumors can spread along several routes, most frequently along the hematogenous pathway, but quite a number follow the lymphatic route and peritoneal seeding (Blanchard et al.).
Of the 450 reported cases, 33.8% had metastasized. Size and gross pathology had some influence on the metastatic rate, but site is most influential (table 14.95). The liver is the most commonly involved site (table 14.96).

Table 14. 95 - Intestinal Leiomyosarcoma
Distant Metastastes according to Pathology
Literature Review by Blanchard et al.

Size			Location	
<5 cm	21/99	21.2%	Duodenum	
5-9 cm	68/187	34.8%		31.3%
10-14 cm	41/105	39.0%	Jejunum	
>15 cm	25/59	42.4%		41.3%
			Ileum	
Position				35.4%
Extraluminal	84/215	39.1%	Meckel	
Intraluminal	16/45	35.6%		16.7%
Both	10/43	23.3%		
Intramural	6/18	33.3%		

Table 14. 96 - Intestinal Leiomyosarcoma
Location of Distant Metastastes (N=118 patients)
Literature Review by Blanchard et al.

Liver	119	46.1% of metastases(')
Lymph nodes	23	8.9%
Peritoneum	33	12.7
Mesentery	26	10.0
Abdomin.Wall	9	3.4
Lungs	8	3.1
Colon	9	3.4
Small Intestine	18	6.9
Generalized	13	5.0
Total	258	100.0%

(') recalculated without local recurrences

Colonic Leiomyosarcoma

Of the tumors reported, 24% metastasized to the liver. Tumors smaller than 5 cm rarely metastasized (Hatch et al.). The sites involved excluding the liver were the lungs, the peritoneum, other parts of the GIT and (rarely) mesenterial lymph nodes. One cecal tumor is reported to have metastasized to the brain and another to the bone of the wrist and several vertebrae.

Of all 74 reported cases, 43% had metastasized, but size was not influential (table 14.97).

Table 14. 97 - Colonic Leiomyosarcoma
Distant Metastases according to size
Literature Review by Hatch et al.

Size	N	Percent with M
0-5 cm	4/11	36.4%
5-9 cm	16/38	42.1%
10-14 cm	6/13	46.2%
>14 cm	6/12	50.0

Anorectal Leiomyosarcoma

Hatch et al. could retrieve 238 reported cases. Of these, 20.2% have metastasized (table 14.98). The liver was the most common site of metastasis, followed by the lungs and the lymph nodes. To the extent that the reports contain sufficient information, metastases in the adrenal, the kidney, the bone, the stomach, the pancreas and other soft-tissue sites are seen. However, as usual, the inaccuracy and incompleteness of the reports do not allow to discern any pattern.

Table 14. 98 - Anorectal Leiomyosarcoma
Distant Metastastes Sites
Literature Review by Hatch et al.

Location		
Liver	20/48	41.7%
Lung	9	18.8%
'Lymph nodes'	5	10.4%
Peritoneum	4	8.3%
Brain	3	6.3%
Prostate	2	4.2%

(Metastases from the uterine leiomyosarcomas are discussed in Chapter 11).

METASTASES from CARCINOIDS

The carcinoids are believed to arise from enterochromaffin cells, scattered throughout the body. The submucosa of the intestine and the bronchi contain most of thse cells. The cells located at the base of the crypts in the intestine are called Kultschitzky cells.
The propensity for metastases to arise differs according to the primary site. This has well been demonstrated in the report of Janson et al. covering 301 consecutive carcinoid patients referred for medical treatment. However, the series seems to be biased as many were already advanced cases, increasing the number of metastatic cases (table 14.99). These data show the proportionally high rate of bone metastases in foregut carcinoids, but without significant difference as far as lymph nodes and liver metastases are concerned.

Table 14. 99 - Carcinoid Tumors
Distribution of distant metastases at referral according to primary site
Modified from data of Janson et al. ,1997

Site	N	LyNo	Liver	Bone	CNS	Skin
Foregut	39					
Bronchial	23	22%	74%	35%	15%	9%
Stomach	13	23	46	--	--	--
Thymus	3	(67)	--	(33)	--	--
Midgut	256	26	76	1	--	--
Hindgut	6	67	100	--	--	--

Bronchial Carcinoids

Distant metastases from bronchial carcinoids seem more frequent than those from the more common intestinal carcinoids. The location at the center of the systemic blood circulation is probably the main reason, as the intestinal carcinoids will remain confined within the abdomen for a longer time.
Specific data on distant metastases from bronchial carcinoids were not found, except for a mention of osteoblastic bone metastases. The most frequent site was the liver (Ducrocq et al.).

One patient was reported by Brown et al. A women with a bronchial carcinoid presented 10 months after surgery with multiple skin metastases, bilateral ovarian and intra-abdominal metastases. Two patients with atypical carcinoids developed skeletal and other metastases concomitant with hypercalcemia within 6 months (Allen).

An unusual metastatic site was reported by Sioutos et al., in a 61-year-old female presenting with pituitary metastases, one year later with intraspinal spread. A similar case associated with several bone metastases had been reported earlier (Rossi et al.).

While a number of breast metastases from GIT-carcinoids have been reported, only one report concerned a bronchial carcinoid primary (Rubio et al.). Aswill be discussed later, skin and thyroid metastases as well as a high proportion of uveal metastases have been reported from bronchial carcinoids.

Table 14.100 - Intestinal Carcinoids
Incidence of Nodal and Distant Metastases
Literature survey by Peplinski

Site	Nodal	Liver
Duodenum	20%	3%
Ileum	35%	10%
Jejunum	35%	10%
Colon	60%	5%
Rectum	10%	10%
Size		
0-1 cm	24%	10%
1-2 cm	75%	18%
>2 cm	83%	31%

Gastro-Intestinal Carcinoids

Small intestine carcinoids are more malignant than appendiceal carcinoids. They first metastasize to the mesenterial lymph nodes. The frequency of lymph node metastases increases with size of the tumor but also with the invasion of the intestinal wall (table 14.100). Liver metastases exhibit the same tendencies.

Intestinal carcinoids usually spread to mesenteric lymph nodes and to the mesentery, sometimes causing chylous ascites. They often metastasize to the liver and less frequently to the lung. Neck nodes have been described.

As many intestinal carcinoids reach a relatively large size, metastatic lymph nodes are very frequent. Some series have reported that liver metastases were present in up to 50% of the patients (Peplinski et al.). A number of cases have been published where other distant metastatic locations occurred either as first sign or in the follow-up.
Based on a literature survey of 1,102 cases, Soga was able to come up with interesting data demonstrating the prominence of intra-abdominal and hepatic metastasis, depending on size and invasion (table 14.101).

Table 14.101 - Carcinoids of Small Intestine
Metastatic rate
Literature survey by Soga 1998

Incidence(‘)		Sites of metastases(“)	
Meckel	28.6%	Lymph node	59.4%
Jejun.ileal	66.2%	Liver	60.0%
Non-append.	37.6%	Mes/Oment/Per	29.2%
All jej.ileal	62.8%	Lung	4.2%
		Bone	3.3%
Size and metastases(°)		**Depth of Invasion/Meta(*)**	
<5 mm	15.8%	Intramucosal	33.3%
6-10 mm	31.5%	Submucosal	30.8%
11-15 mm	74.6%	Muscular	37.8%
16-20 mm	72.6%	Transmural	68.4%
21-30 mm	86.9%	In neighb.struct.	79.2%
31-40 mm	72.0%		
41-50 mm	47.6%		
>50 mm	65.7%		
All	57.9%		

(‘) based on 1,062 cases; (“) 667 cases; (°) 428 cases; and (*) 482 cases.

Progression

An impressive study on progression has been provided by Makridis et al. They followed 121 patients with relatively advanced midgut carcinoids after first surgery and various medical treatments. Quite a number needed a second or even third operation.
Of the few patients presenting without metastases and those ‘completely’ debulked, only 25% developed metastases. The rate for new metastases to the liver was quite high (21/37) for patients with mesenteric metastases, but they rarely developed (only 3) extra-

abdominal metastases. Patients with 'liver only' metastases frequently developed (60%) extra-abdominal metastases, though mesenteric metastases at a lower rate. When mesenteric and liver metastases were present, extra-abdominal metastases were also frequent (13/59). This is shown in diagram form in fig. 14.14.

The mean time for progression differed according to the metastatic status:

no metastases present :	12.0 yrs
mesenteric metastases:	6.2 yrs
liver only metastases:	4.5 yrs
mesenteric and liver :	4.8 yrs.

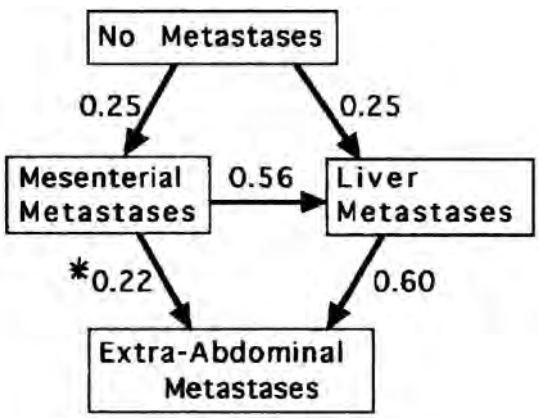

Fig.14.14 - Metastatic progression of Midgut carcinoids after first treatment (N=121,
(*) the figure includes patients with liver and mesenteric metastasis (Redrawn from Makridis,1996)

Spread - Metastases

Carcinoids may metastasize widely. No autopsy studies nor reviews on the subject are available in the literature.

Bone Metastases

There is a definite correlation between bone metastases and the location of the primary carcinoid. They are common in foregut and hindgut tumors but rare in midgut carcinoids. There are no differences in the metastases distribution between bronchial and intestinal carcinoids (fig. 14.13). Bone metastases may be mixed osteoblastic and osteolytic in the same patient. Widespread bone metastases without bony symptoms are not uncommon (Manoli et al.). One case of bone metastases in the cervical column revealing a pancreatic carcinoid has been reported (Troussier).

Bone metastasis are usually osteolytic, but some osteoblastic ones have been reported (table 14.102).
Bone metastases from thymic carcinoids (Georgy et al.) have also been reported.
Two cases of metastatic carcinoids (M50 and F65) both presenting with bone metastases and hypercalcemia, metastatic from bronchial carcinoids, have been reported. Both had other metastases as well. We are not aware of similar also reports mentioning hypercalcemia in carcinoid bone metastases, but when one institute is able to report on two cases, it must be more common than generally believed.

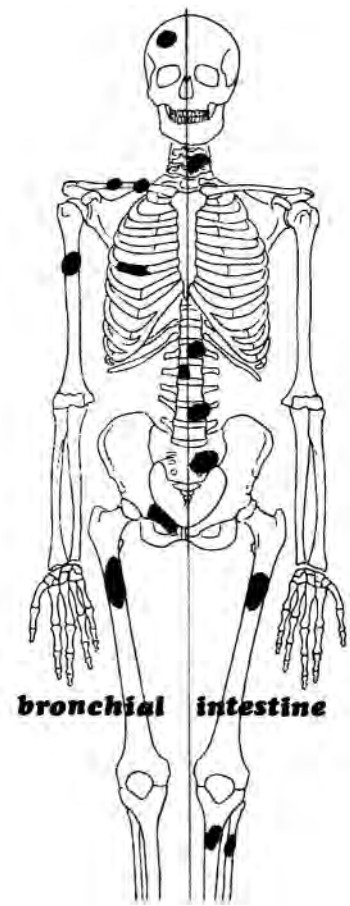

Fig.14.15 - Distribution of bone metastases from bronchial (left) and intestinal (right) carcinoids. (drawn from literature data collected by Powell,1988.

Table 14.102 - Carcinoids
Reports on Osteoblastic Metastasis

Author	Pat	Primary	Site of M	Interva
Hyman 1964	M50	Bronchial	Ribs-spine-pelvis-	?
Hyman 1964	F55	Bronchial	Clavicle-Pelvis	4 mo
Thomas1968	F50	Intestine	T4-T8-Ilium	Simult
Thomas 1968	M47	Rectum	Spine- Femur	?
Peavy 1973	M67	Bronchial	Diffuse	7 yrs
Peavy 1973	F43	Bronchial	Thorax	Simult
Fishman '76	M25	Mediast.	Skull-ribs-Spine	6 mo
Ashraf 1977	M48	Bronchial	Clavicle-Spine-Sternum	7 mo
Manoli 1980	M55	Rectum	Widespread	Simult
Manoli 1980	M40	Unknown	Widespread	---
Norman 1981	F27	Bronchial	Clavicle	12 yrs
Johnson 1982	F56	Bronchial	Femur	6 yrs
Troussier '88	M63	Pancreas	C1-C2	Reveal
Giordano '94	M46	Foregut	Widespread	Reveal

Metastases to the Skin

Skin or subcutaneous metastases may either be the initial manifestation of a midgut or of a pulmonary carcinoid, preceding it by many years, but they can also occur several years after surgery for the primary (Krausz et al.).

Ophthalmic Metastases

Ophthalmic metastases are not uncommon. The occurrence of orange choroidal lesions should raise suspicion of carcinoid metastases and prompt questioning about previous surgery and a search for systemic spread, as these metastases are usually not solitary (Hykin et al.).

In 1990, Fan et al. collected 22 cases of carcinoid metastases in the choroid and one to the ciliary body and choroid, two to the ciliary body, one to the iris, two to the iris and ciliary body. Of these 28 uveal metastases, 24 were from a bronchial carcinoid, two from the ileum, one from the esophagus and one from a thymic carcinoid.

Table 14. 103 - Bronchial Carcinoids
Ophthalmic Metastases

Author	Patient	Site of Meta	Interval
Font 1966	F74	Ri.Choroid	3 yrs
Walker 1974	F38	Bilat.Choroid	4 yrs
Bell 1975	F29	Le Choroid	2 yrs
Rodrigues '78	M54	Ri.Iris	(')
Riddle 1982	M47	Le.Choroid	9 yrs
Riddle 1982	M49	Ri.Iris	5 yrs
Riddle 1982	F12	Ri.Choroid	7 yrs
Riddle 1982	F26	Le.Choroid	3 yrs
Riddle 1982	F74	Ri.Choroid	2 yrs
Riddle 1982	F13	Choroid	1 yr
Riddle 1982	M16	Choroid	7 yrs
Archer 1982	F28	Iris	9 yrs
Balestrazzi '89	F37	Choroid	6 yrs
Bardenstein '90	M50	Ri.Ciliary Body	20 yrs
Nida 1992	M63	Ri.Orbit	(")
Harbour 1994	M55	Uveal	60 mo
Harbour 1994	F48	Uveal	55 mo
Harbour 1994	F55	Uveal	simult
Harbour 1994	F26	Uveal	5 yrs
Harbour 1994	F68	Uveal	simult
Harbour 1994	F52	Uveal	15 yrs
Harbour 1994	M48	Uveal	simult
Fan 1995	M48	Bilat.Choroid	simult
Fan 1995	F52	Le.Choroid	simult
Fan 1995	F58	Bilat.Choroid	7 yrs
Hykin 1996	F23	Bilat.Choroid	8 yrs
Perri 1998	M32	Bilat.Choroid	13 yrs
Kreusel 1998	M65	Ri.Choroid	Simult.
Fajnkuchen '98	F18	Bilat.Choroid	5 yrs
Eagle 2000	F77	Le.Choroid	Reveal.

(') only radiologic evaluation of the thoracic tumor
(") preceded diagnosis of bronchial primary with 4 years

The same authors collected 22 cases metastatic to the orbit. Twelve of them were ileum primaries, one from the mediastinum, one from colon and one from the trachea, but in seven cases the primary was not reported. It should be noted that bronchial carcinoids metastasize to the choroid, whereas intestinal ones regularly metastasize within the orbit. There was one additional case with metastasis in the optic nerve from a mediastinal carcinoid.

Table 14. 104 - Non-Bronchial Carcinoids
Ophthalmic Metastases

Author	Pat	Primary	Site of M	Interval
Rush 1980	F58	Colon	Orbit	1 week
Harris 1980	F??	Ileum	M.Rectus	(")
Riddle 1982	F66	Ileum	Orbit	5 yrs
Riddle 1982	M51	Ileum	Orbit	1 yr
Riddle 1982	F76	Ileum	Le.Choroid	1 yr
Riddle 1982	F71	Trachea	Orbit	2 yrs
Krohel 1982	F65	Ileum	Orbit	3 yrs
Shields 1987	F63	Ileum	Ri.Orbit	7 yrs
Braffman 1987	F67	Ileum	Ri.Orbit	12 yrs
Shetlar 1990	M51	Ileum	Le.Orbit	3 yrs
Shetlar 1990	F71	'Intest'	Le.Orbit	5 yrs
Shetlar 1990	F38	(Ovary)	Ri.Orbit	9 mo
Harbour 1994	M62	Esoph.	Uvea	simult
Harbour 1994	M37	Thymus	Uvea	simult
Fan 1995	F45	Ileum	Ri.Choroid	9 yrs
Fan 1995	M51	Ileum	Le.Orbit	simult
Fan 1995	F58	Colon	Ri.Orbit	simult

(") the metastasis was diagnosed 2 years before the primary was found at autopsy

In a few cases, eye metastases presented before the diagnosis of the primary, but on an average 4 years after the diagnosis. They occurred twice as often in women as in men.

Ophthalmic metastases are frequent in bronchial carcinoids (table 14.103). Table 14.104 lists those from the non-bronchial carcinoids.

A small caruncular mass at the left eye was found to be a metastatic carcinoid, probably from an ileal primary (Grotz et al.).

Head and Neck Metastases

Head and neck metastases are very rarely from bronchial carcinoids (table 14.105).

One patient with tonsillar metastases from a pulmonary carcinoid presenting two months after resection was reported by Linton et al. No other such cases have ever been reported.

One case to the mandible, one to the soft palate (Mintz) and one bilateral in the parotid gland have been reported (Dilkes et al.).

Table 14.105 - Carcinoid Metastatic to H&N region
Cases Reported

Author	Pat	Primary	Site of M	Interval
Gremillet '77	F24	Bronchial	Gingiva	6 mo
Mintz 1988	F71	Bronchial	Palate	Revealing
Dilkes 1991	F64	Bronchial	Parotid	3 yrs
Linton 1998	M47	Bronchial	Tonsil	Revealing

Metastases to the thyroid have been reported from

small bowel or rectal carcinoids, but also from a bronchial carcinoid (Krausz et al.).
Metastases within the thyroid are thought to be rare, but it is possible that some have been reported as medullary cancers (Matias-Giu et al.). Of the eight reported, two were from rectum, four from the small bowel, one from the stomach and one from the lung. Matias-Giu added six cases in whom it was the first manifestation of a carcinoid. All were women, 4 from a broncho-pulmonary carcinoid and one abdominal. In one no primary carcinoid was found. Later, in 1996, Chico et al. reported on two cases where a thyroid nodule of 'atypical' nature, one first interpreted as medullary carcinoma, preceded the finding of a bronchial carcinoid.
Recently, four cases from a bronchial and one from a thymic carcinoid were reported by Leboulleux et al.
Differential diagnosis with the rare ectopic thymic carcinoid within the thyroid is necessary, like the case (F26) reported by Inzucchi et al.

Metastases to the Breast

Breast metastases are occasionally reported. Rubio et al. collected 13 cases from the literature, 11 of which were from the GIT-tract. They pose the problem of differentiation from a breast primary, particularly those with some neuro-endocrine differentiation (Azzopardi et al.). Review of the case reports highlights the fact that many times, the breast tumor was reported as an undifferentiated, small cell or medullary carcinoma. The rarity of the occurrence of metastatic carcinoid compared with carcinoid metastases does not rise sufficient suspicion of a metastatic disease, compared with metastasis from other primaries. Information on past history is essential for the pathologist, especially frozen sections.

Table 14.106 - Carcinoids
Cases Reported with Breast Metastases

Author	Pat.	Site of Primary	Interval
Harrist 1977	F58	Bronchial	19 yrs
Warner 1980	F47	Bronchial	Revealing
Schurch 1980	F53	Ileum	Revealing
Harris 1981	F54	Ileum	6 mo
Kashlan 1982	F69	Ileocecal	Simult.
Krohel 1983	F65	Ileum	3 yrs
Ordonez 1985	F41	Pancreas	2 mo
Ahlman 1986	F71	Ileum	6 mo
Landon 1987	F46	Ileum	7 yrs
DiPalma 1988	F54	Ileum	Reveal
Lozowski 1989	F66	Ileum	6 yrs
Oleksowicz '90	F60	Bronchial	Reveal
Barreau 1992	F42	Appendix	1 yr
Moir 1993	F63	Bronchial	28 yrs (!)
Fishman 1994	F52	Ovarian	1year
Wozniak 1998	F47	Bronchial	Revealing
Kaltsas 1998	F23	Ileocecal	Revealing
Kaltsas 1998	F20	Bronchial	3 yrs

Mammographic images appear not to be specific and detect the difference, though the regular contour is described in many reports. Specific imaging with radio-octreotide (SRS) may help pinpoint the diagnosis in the patients with a known carcinoid (Kaltsas et al.).
Reviewing the literature in 1992, Barreau et al. retrieved 5 cases reported before 1977. The first report on primary carcinoids of the breast was presented by Cubilla et al. on 8 patients.
For this metastatic site, there is no obvious preponderance of bronchial carcinoids (table 14.106). The interval ranges from revealing cases to as long as 28years. The carcinoid syndrome was present in a number of patients, demonstrating the presence of liver metastases.

Metastases to the Central Nervous System

In the experience of Patchell et al., epidural spinal cord compression was the most frequent neurological complication (table 14.107). Of their 14 personal cases, 5 were from a bronchial primary. In two patients it was the first manifestation of a carcinoid. In half of the patients the involved vertebra was thoracic. Other cases have been since reported (table 14.108).

Table 14.107 - Carcinoids
Metastatic Complications
Modified from Patchell et al. (1986)

	L-case(')	P-cases(')
Epidural Cord Compression	7	14
Brain Metastases	4	12
Base of Skull metastasis	--	1
Dural metastases	4	--
Leptomeningeal	1	1
Peripheral nerve lesions	--	5
Recurrent laryngeal nerve palsy	--	3
Brachial plexus Metastases	--	2

L: literature, P: personal cases

Table 14.108 - Carcinoids
Complicated by Spinal Cord Compression

Author	Pat.	Primary	Site of M	Interval
Ansink 1984	F64	Intestine	L3(')	2 yrs
Poole 1985	F56	Ileocecal	T2-T4	3 yrs
Saleh 1987	M65	Ileum	T6-T7	6 yrs
Wawman 1993	M59	Thymus	T6-T7	2 yrs
Waldherr 2000	M45	Bronchial	T12	6 yrs

The same authors had 12 cases of intracranial metastases, contrasting with the low number reported in the literature at that time. The lesions were multiple in 5 and two single lesions were in the pituitary. In one patient, the diagnosis of brain metastases antidated the diagnosis of the primary (not given).
Since 1966, only 5 cases of brain metastases have been reported, among them one from a colonic primary (Ozawa et al.)..

Huang et al. have reported on a case with one large dural metastasis mimicking a meningioma The patient (M50) had an esophageal carcinoid diagnosed

9 months previously.
Three other patients have been reported with intradural metastases. After surgery for a thymoma 17 years previously, a patient aged 53 presented with a pancreatic carcinoid, followed 3 years later by a large lobulated intradural mass at L2-L3, diagnosed as carcinoid (Rao et al.). Previously, Greco et al. had reported on a patient (F66) operated on for a bronchial carcinoid developing progressive perineal pain in the following months.
Another patient (M60) was reported by Gowitt et al. He underwent a laminectomy for an epidural mass T4-T6 encroaching the spinal cord, carcinoid at histology, but no primary was found.
The case (M61) reported by Hussein et al. presented with bilateral frontal headache. Various investigations were non-conclusive, but at autopsy a bronchial carcinoid was found, complicated by extensive liver metastases. Several nodules were found over the internal surface of the dura.

Three cases of leptomeningeal metastases have been reported (table 14.109). The case-report of Schiffman is entitled 'metastasis to the brain', but the description is clearly meningeal.

Table 14.109 - Carcinoids
Cases with leptomeningeal metastases

Author	Patient	Primary	Interval
Schiffman 1982	F62	Cecum	5 mo
Nagourney 1985	F67	'Abdominal'	1 yr
Patchell 1986	??	??	??

Vocal cord paralysis was caused by intrathoracal primary carcinoids (bronchial or thymic) with involvement of the recurrent laryngeal nerve. The brachial plexus involvement was probably secondary to metastatic cervical nodes.

One case metastatic in a prolactin secreting adenoma, another in a pituitary adenoma and one in a meningioma have been reported (review by Abe et al.).

Ovarian Metastases

Robboy et al. (1974) have reported on 35 cases, where in 10 cases the metastases were only found at autopsy. The indication for laparotomy was an adnexal mass or another abdominal symptomatology. In two cases, the diagnosis of a primary was known, in 11 it was identified at surgery. In 7 it was disclosed at histology and in 4, only strongly suspected in the absence of histology. The primary was abdominal in all, but in all segments of the intestinal tract, mainly the ileum.
Brown et al. have reported one case (F48) from a bronchial carcinoid, presenting one year after surgery with several cutaneous nodules and an adenexal mass.

Two cases of bilateral ovarian carcinoids have been reported, found simultaneously at laparotomy with an appendiceal primary (Heisterberg et al.).

Cutaneous Metastases

A few reports on this rare metastatic site have appeared. It is remarkable that they virtually concern only female patients, three with metastases to the scalp. The metastases present usually as a small multi-nodular elevated cutaneous mass, either single or multiple (more than 10) (table 14.110).

Table 14.110 - Carcinoids
Cutaneous Metastases -Cases Reported

Author	Pat	Primary	Site of M	Interval
Keane 1980	F57	Bronchial	Thigh	6 yrs
Brown 1980	F48	Bronchial	Scalp-Abdomen	1 yr
Terzakis 1984	M51	Bronchial	Flank	Simult
Archer 1985	F68	(Liver meta)	Multiple Scalp,trunk, thigh	---
Rodriguez '92	M80	Gastric	Multiple Forehead, neck, arms,trunk, thigh	Simult
McCracken '96	F67	Colonic	Eyelid	1 yr
Ereno 1997	F72	Larynx	Scalp(mult.)	Simult

Reviewing the literature on bronchial carcinoids metastatic to the skin, Keane et al. found 9 of them reported, 6 being female patients. The site of the metastasis was not reviewed.
Umbilical metastases as revealing sign of widespread intra-abdominal metastases from a carcinoid have been reported (Lopez-Soto et al.;Grunewald).

Non-erythematous subcutanous nodules appeared successively all over the thorax and arms in a patient (F60). Histology showed an undifferentiated carcinoma, while a mammography also revealed multiple nodules. In spite of hormono-chemotherapy, the pathology progressed. Eventually, a nodule in the pulmonary nodule disclosed a carcinoid, similar to the other, after histology was reviewed (Oleksowicz et al.). Other patients have been reported as having subcutaneous nodules in the follow-up.

CARCINOID HEART DISEASE

The heart can be implicated in carcinoid disease in several ways:
A.Endocardial disease such as
-- right-sided valvular disease, frequently tricuspid regurgitation and pulmonary stenosis;
-- left-sided valvular disease (aortic and/or mitral);
-- restrictive cardiomyopathy.
This pathology could well arise by release within the heart cavities of PDGF from serotonine-rich platelets, as they are mechanically destroyed within the heart.

B. Metastatic myocardial disease within atrium or ventricle. The first report of patient was by Pellikka et al. Only three cases from an ileum primary and two of a bronchial primary have been reported (Drake et al.).

Schiller et al. reported moreover a patient with gall-bladder carcinoid that had metastasized within the interatrial septum, which is devoid of myocardial cells. Recently one patient was reported as having widespread metastasis including in the left ventricular myocardium, without any valvular involvement (Davis et al.). In another patient, a M33, a rather large mass was found in the left ventricle, preceding by 6 months the finding of a probably primary pancreatic cancer, both at histology an atypical carcinoid (Hennington et al.).
A right hemicolectomy was done in a patient (M54) in whom fortuitously a mass was found in the right fossa iliaca, which turned out to be a carcinoid of the distal ileum. Five years later, ventricular arrhytmia was observed and a large ventricular mass found by means of echocardiography and SRS-scintigraphy (Yeung et al.).

C. Pericardial disease with pericardial effusion was noted in 9 of the 39 (23%) patients with carcinoid syndrome who had cardiac involvement (Moyssakis et al.). Other authors refer to 50%.

D. Vascular involvement such as in coronary sinus and aorta.

E. Valvular involvement:
In carcinoid heart disease, the lesion is the carcinoid plaque, a smooth, glistening whitish gray elevation. Its distribution is more often on the right side of the heart and it is frequently seen on the endocardial surface of the right atrium and ventricles as well as on the pulmonar and tricuspid valvular leaflets. Right valvular heart involvement, when present, is often severe. It occurs in 45% of the patients presenting with the carcinoid syndrome (Moyssakis et al.).

Uncommon metastasis

Falk et al. have reported on a M56 presenting with typical carcinoid complaints, where at CT a large hepatic metastasis was found associated with multiple (more than ten) metastases within the spleen. Another patient (M49) was reported by Takada et al. as presenting with a solitary spleen metastasis eight years after surgery for a bronchial carcinoid.

Peritoneal metastases have not been discussed frequently in the literature. They are probably part of a widespread intrabdominal involvement in cases of ileal carcinoids. Robb et al. have reported on two cases where at laparotomy (M77) peritoneal metastases was found secondary to a large pancreatic carcinoid, and in another patient (M43) from an unknown appendiceal primary.

Rare cases of metastasis in the thyroid, the pancreas, the orbit, the lacrimal fossa, the choroid and the optic nerve have been reported.
In a M25, metastases of an 'unspecified' nature in the supraclavicular and mediastinal nodes were found. Six months later he developed osteoblastic metastases and blurred vision. Autopsy disclosed a carcinoid in the mediastinum as probable first site and the presence of metastasis in the optic nerve (Fishman et al.). A rectal carcinoid (M79) with metastases to the larynx, pancreas, adrenal glands and brain was recently reported by Danikas et al.

Diagnosis

While the diagnosis can be presumed in a minority of the patients on the basis of the flushing syndrome, the diagnosis has to be made on surgical pathology examination of a biopsy or of the resected tumor. High serum-serotonin levels are very indicative of a metastatic carcinoid, but only some of the patients will have symptomatology sufficient to raise suspicion of a metastatic carcinoid.
Percutaneous needle biopsy with radiological guidance will confirm the diagnosis of any carcinoid tumor and/or of its metastases. Surgery is the mainstay of the diagnosis and the treatment.

Imaging

Some imaging procedures can be helpful in outlining extension of any primary and possibly show metastases, when the diagnosis of a primary carcinoid has been made.
Angiography of hepatic metastases produces characteristically highly vascular and dense deposits. They are usually widespread and appear as one or several large areas of confluent tumor blush or as multiple rounded vascular nodules (Kinkabwala et al.).

Isotope scintigraphy has been developed in the last decades. Due to the molecular analogy with adrenaline and serotonin, meta-iodo-benzyl-guanidine (MIBG) labeled with ^{131}I was first applied, with relatively good results. The best images are obtained after 24-48 hrs. About 50-70% of the tumors can be visualized. Liver metastases are difficult to be outlined against the normal liver activity, but CT certainly scores better. It is significant that:

(1) no false-positive images are obtained;
(2) some metastases not visualized by other imaging procedures, are being detected;
(3) in patients showing good uptake, the radiopharmaceutical could be used for therapy, as has been done for neuroblastomas, even for liver metastases (Prvulovich et al.).

The MIBG procedure is not specific for carcinoids as other neuroendocrine tumors can be visualized too.

Somatostatin-receptor imaging (SRS) has been developed In recent years. Octreotide was the first, but could not be labeled adequately for imaging studies. The third amino acid was then changed from phenylalanine to tyrosine and labeled with ^{131}I. This

permitted adequate tumor-imaging studies. The drawback was, however, its excretion by the hepatobiliary system, resulting in difficult abdominal interpretation, the earlier images being then the only adequate in clinical evaluation.

When DTPA was placed on the N-terminus of the D-phenylalanine moiety, labeling with In-111 become readily possible (fig. 14.16). This radiopharmaceutical is now being studied in a very large variety of neuroendocrine tumors.

Various authors have shown that for carcinoids somewhat more tumors are visualized than using MIBG although a 100% sensitivity has certainly not been reached. False-positive images are, however, not seen. Kwekkeboom et al. showed that octeotride scintigraphy, alone or with other imaging methods, led to the detection of more tumor sites than with other imaging techniques.

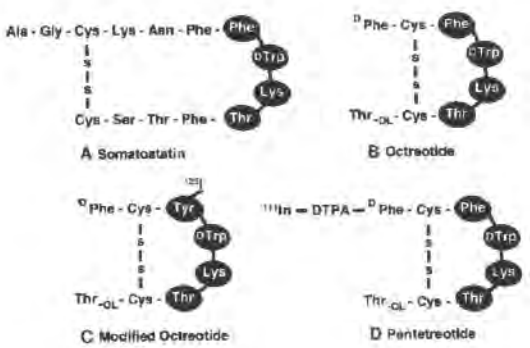

Fig.14.16 - Molecular structure of Somatostatin (A) and of the subsequently derived analogues utilized for scintiscanning of carcinoid tumors: octreotide (B), I-123-Tyr-3-Octreotide (C) and 111-In-DTPA-D-Phe-1-Octreotide or Pentatreotid (Octreoscan) (D) (Olsen et al., with permission)

This means that for a group of 100 patients 65 extra lesions may be detected. The multicenter study by Olsen et al. (table 14.111) reported a high true positive rate (78%), but also a high proportion of consistency (80%).

Table 14. 111 - Somatostatin - Receptor Scintigraphy
Overview of Multicenter Results (Olsen et al.)

for 237 carcinoids	
True Positive	185 (78%)
True Negative	5
False Positive	0
False negative	47 (20%)
Unconfirmed-Positive	41 (17%)
Proportion Consistent	190/237 (80%)

The detection of these unknown sites is essential for further treatment. It localizes tumors and provides a basis for decisions about surgery, medical treatment or radiotherapy. Unneccessary surgery can then be avoided or surgery directed to resect metastases at an 'earlier' stage.

Some authors have concluded that MIBG and octreotide or somatostatin receptor imaging (SRI) are complementary, as both methods also show uptake in tumors not visualized by the other isotope. In an overview of the results, Öberg proposed the most appropriate procedure for diagnosing GIT carcinoids (table 14.112).

Table 14.109 - GastroIntestinal Carcinoids
The probably most appropriate procedure (Öberg)

FOREGUT		
p.CgA		Pulmonary X-ray
U.5.HIAA		CT
u-histamin met.abolites		Gastroscopy
p.ACTH, GHRH,pCRF		Octreoscan
		PET (C-11-5HTP)
MIDGUT		
p.CgA	Pentagastrin	Octreoscan
U.5-HIAA	stimulation test	PET (C-11-5HTP)
p.NPK	of NPK, subst.P	Barium enema
		CT,MRI, US
HINDGUT		
p.CGA		Octreoscan
s.HCG α/β		CT.MRI,US
s-PP		Colonoscopy

p.CgA: plasma Chromogranin A; u: urine, s: serum; NPK: neuro-peptide K; PET: positron emission tomography; pCRF: plasma-corticotrophin-releasing factor.

For carcinoids of the lung, Oliaro et al. recently confirmed high sensitivity in localizing the tumor and its recurrences or their metastases. The predictive value for responsiveness to 'cold' octreotide therapy will be discussed below.

SPECT techniques seem also to improve the accuracy of SRS in abdominal carcinoid tumors (Schillaci).

Scintigraphy provides information on the tumor biology, the size and the location of the malignancy.

More data have now accumulated. Kälkner et al. were able to conclude from a study of 100 carcinoid patients that

- a positive octreotide SPECT- scintigraphy correlates with elevated levels of urinary-5HIAA and plasma-chromogranin A,
- a high tumor/background ratio correlates with high hormone production in untreated patients,
  Both can be used to determine the degree of differentiation of the tumor and may be of prognostic value.
- treatment with a somatostatin analogue or even IFN increases the tumor/background ratio, indicating an up-regulation of somatostatin receptors.

A molecule derived from 5-HTP, a metabolite of serotonin, has recently been labeled with ^{11}C in the β-position, to be used in Positron Emission Tomography (PET). According to Eriksson et al., it could detect many more carcinoid lesions than CT and

readily demonstrates the primary and its metastases in the liver, bone, lymph nodes and pleura.

Metastases from Carcinoids at Particular Sites

Primary carcinoids can occur in different organs, but are indeed very rare.
Reports or review on metastases of carcinoids in a particular sites are absent from the literature, with the exception of a review of gallbladder carcinoids by Yokoyama et al. (table 14.113). Of the 29 cases retrieved from the literature, 15 had adequate data. The largest number of metastases was found in the liver, but how far these are contiguous or true metastases can not be evaluated.
We are aware of two cases presenting with a chylothorax (Graham et al.; Johnson et al.).

Table 14.113 - Carcinoid of the Gallbladder
Metastatic sites reported (N=15)
Review by Yokoyama et al.

Liver	12	Small bowel	1
Lung	4	Stomach	1
Adrenal	4	Heart	1
Abdomin.Nodes	4	Pancreas	1
Bone	3	Diaphrgagm	1
Spleen	2	Brain	1

METASTASES from EXTRA-PULMONARY SMALL CELL CANCERS

Small-cell cancers (EPSCT) originating outside the lungs are rare. The tumor is locally aggressive, like its pulmonary counterpart, and distant metastases are common. The literature is replete with case reports and small series, providing more information about diagnosis, pathology and outcome of treatment.

Information about distant metastases is rarely given in the reports. A few small series and reviews give some data, but it is almost impossible to detect any trend or pattern (table 14.114). Although there are some difference, the small numbers does not allow further conclusions.

Pierce et al. have reviewed the literature for head and neck-EPSCT (table 14.115). It is difficult todetect any specific pattern or differences, but the lungs, liver and bone are apparently the most frequently involved sites. Ampil et al. have reported on a woman (F37) presenting with spinal cord and cauda equina compression, in whom at examination a tumor of the uterine cervix was found, a small-cell carcinoma.

Table 14. 114 - Extra-Pulmonary Small Cell Tumors
Distant Metastases in some series

	ES(1) N=11	ES(2) N=11	Sto(3) N=17	Cervix(4) N=11
Lungs	--	--	7	2
Bone Marrow	3	--	--	--
Liver	1	7	14	1
Peritoneum	1	--	--	--
Duodenum	1	--	--	--
Adrenal	2	--	--	--
Pelvic	--	--	--	7
Abd.nodes	--	5	7	2
Diaphragm	--	1	--	--
Bone	1	3	1	1
Brain	--	--	6	--
Skin	--	--	2	--

ES:esophagus, Sto: stomach;(1) Nichols et al. 1989; (2) Beyer eyt al. 1991; (3) Matsui et al.1991; (4) Sykes et al. 1999

Table 14. 115 - - Extra-Pulmonary Small Cell Tumors
Distant Metastases in H&N- locations
Data of Pierce et al.

Site	Sino-Nasal N=33	Salivary Gl. N=28
Lung	2/33	4/28
Liver	2	3
Bone	3	2
Brain	--	3
Adrenal	1	2
Other	5(')	7(")
Lymph node	3	3
Multiple	5	6
Single	2	8
Total with	12	14

(') mediastinum, bone marrow, skin, kidney
(")mediastinum, spleen, skin, breast, abdomen, bone marrow

References

Caution: References are given for documentary purposes. Not all have been reviewed or used in the redaction of the text. We do not claim completeness of data. The references are as much as possible grouped per subject heading. For some headings, only reports after 1974 are listed.

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EPILOG -OVERALL LESSONS

Ubiquity

Cancer can manifest itself in various different ways. This also applies for the metastases. Firstly, they can appear before the patient is aware of any sign or symptom of the primary is acknowledged. They can appear anywhere in the body at visible or hidden sites, sites visible only to imaging techniques, but also at unusual sites far from the primary. The first physician consulted may not have the clinical oncological experience and knowledge to be able to make a judgment, and the patient should be referred to an experienced oncologist, whose first task is a thorough anamnesis and clinical examination. The responsability of the pathologist to whom cells or tissue is submitted is heavy in order not to misroute the patient towards an unappropriate treatment.

Seed and Soil - Pathway and Flow

Well known is the adagio 'seed and soil'. They are indeed the factors influencing the final settlement of the metastasis. The malignant cells will have to travel some distance along arterial, venous or lymphatic vessels in order to reach te next site. This is a non-random process, governed by vascular anatomy of the primary organ, its situation within the vascular network and for venous circulation by the direction of its flow. The anatomical relationship between the organ with the primary tumor and the recipient organ is a crucial factor in the selective distribution of the metastases. As such, pathway and flow represent another two factors. This has been highlighted various times throughout this book.

Data Banks - Clinical Trials

The enrolment of hundreds of patients in therapeutic trials should not neglect the observation and registration of metastatic disease. These data banks are used apparently only to obtain academic knowledge on the factors influencing treatment results. They are in fact gold mines as they surely contain many hidden information on the pattern of several metastatic locations as within the liver, lungs and bone, as well as the multiplicity of metastases, the timely appearance and progression. Coordinators of the trials should transfer those patients towards an appropriate data-bank or follow-up registers for further studies on the metastatic process. The oncological community is still in need of data on metastasis, mainly anatomical distribution, patterns and dynamics.

Reporting

Publishing unusual cases is not only worthwhile, but they should be correctly and adequately reported. Adequate information includes correct histological reporting as well as the dates of procedures and diagnosis and will permit later reviewers to collate the data.

The report should be given an apropriate title: for example 'Cancer of the kidney with a revealing metastasis in the orbit', is to be preferred above 'A metastatic orbi-tal tumor from a renal cell cancer.' This will ensure better indexing and retrieval from literature data banks. Literature review should pertain to the subject and not to brain metastases in general, when discussing a rare case of brain metastases from an uncommon site.

A report entitled as 'Metastatic renal cancer', creates the expectation that metastases from a renal cell cancer will be discussed and not, as it turned out to be, metastases to the kidney.

Another example is 'Metastases of central nervous system neoplasms'. The article turned out to be a discussion of metastases of extra-cerebral tumors into intracranial neoplasms. In view of such examples, even the most trained indexer may misclassify the articles, making them impossible to be correctly retrieved.

Editors of journals should check titles as well as they check the text. Long titles with three lines should be avoided.

ILLUSTRATION CREDITS

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