Derek C. Allen

Histopathology Reporting

Guidelines for Surgical Cancer

Second Edition

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To Alison, Katie, Rebecca, and Amy

Preface to the second edition

Many of the introductory comments in the first edition of this book regarding the increasingly focused approach required of pathologists to surgical cancer histopathology reports still pertain. In the intervening period a number of trends have continued to develop that have required an update.

- system-specific cancer multidisciplinary meetings with specialized clinicians and appropriate pathological, radiological and oncological support. Increasingly these meetings require fewer pathologists reporting significant numbers of relevant cases rather than a large number of pathologists reporting them only sporadically. From this has arisen cancer-specific lead pathologists encompassing a spectrum of specialist differentiation from "monospecialists" to "generalists with an interest in" and variations in between. Cancer report datasets aimed at maintaining overall standards of reporting are freely available published by various bodies, viz the Royal College of Pathologists, the Association of Directors of Anatomic and Surgical Pathology and the College of American Pathologists. In the UK the Royal College Datasets are a model for standardized reporting and their success is measured by their ongoing revision and second cycle of publication. No doubt specialist and team reporting will increase, particularly as the parameters for each cancer type report become more complex. Datasets with their notes and attendant information are required not only to update pathologists but also to keep them aware of significant pathology in other areas that might impact on their own specialization, e.g. metastatic carcinoma. Availability as PC-based templates also facilitates reporting, audit and download to cancer registries.
- in immunohistochemistry there is an ever-expanding range of increasingly robust antibodies which, with antigen retrieval methods, are applicable to surgical histopathology material. Panels of these antibodies not only help to identify the tumour type and subtype but can also give prognostic information as to the likely biological outcome and response to hormonal or chemotherapy. The data change rapidly, often with supposedly cancer type-specific antibodies becoming less so with time but still useful in combination with other putatively positive and negative markers in a panel. It can be difficult for the pathologist to

keep abreast of current information in this field and which antibodies to use that will give reliable results.
- increasing multi-professional team working in the laboratory necessitates provision of core information to Biomedical Scientists as a basis for why we do what we do and how we do it in reporting surgical cancer histopathology specimens, particularly in relation to supervised role delegation such as specimen dissection. This knowledge base is also necessary to students and trainees, given the changes that have occurred in the undergraduate medical curriculum, in postgraduate medical training and the pressures on academic pathology.
- the 6th edition UICC TNM Classification of Malignant Tumours and the 5th edition UICC TNM Atlas have been published.

This text aims to augment and complement dataset reporting for surgical cancer histopathology specimens. Hopefully it highlights the main diagnostic and prognostic criteria for the common cancer types but also provides diagnostic clues for differential diagnoses and characterizes typical immunophenotyping. The author gratefully acknowledges the use of illustrations from Wittekind C, Greene FL, Hutter RVP, Klimpfinger M, Sobin LH (eds) TNM Atlas: Illustrated Guide to the TNM/pTNM Classification of Malignant Tumours. 5th edition. Springer. Berlin Heidelberg 2004.

I would also like to express my appreciation of the support from my colleagues at the Belfast City Hospital Histopathology Laboratory and thanks to my co-authors in Derek C Allen, R Iain Cameron (eds) Histopathology Specimens. Clinical, Pathological and Laboratory Aspects. Springer. London 2004 – Tong Fang Lioe, Sèamus Napier, Roy Lyness, Glenn McCluggage, Declan O'Rourke, Maurice Loughrey, Damian McManus, Maureen Walsh, Kathleen Mulholland, Richard Davis, Lakshmi Venkatraman and Peter Hall.

Thanks also to Melissa Morton, Eva Senior and the staff at Springer, my secretary Michelle McLaughlin (I don't know how you read the writing!), and, last but most of all, my wife Alison and our girls Katie, Rebecca and Amy.

Derek Allen
Belfast

Preface to the First Edition

Current reorganization of cancer services has emphasized the need for higher quality standardized histopathology reports on surgical cancer specimens. Increasing clinical subspecialization is demanding detailed histopathology reports which are inclusive of multiple diagnostic and prognostic data directly relevant to the clinical management of each cancer type in individual patients. It is increasingly difficult for the consultant or trainee pathologist, surgeon or oncologist to recall those facts most salient to each cancer type, particularly if they are practising across a number of subspecialties and are generalist in remit. From this have arisen standardized or minimum dataset reports as a practical educative and reporting aid for surgical histopathology specimens. This approach is being actively pursued by various national bodies such as the Royal College of Pathologists (UK) and the Association of Directors of Anatomic and Surgical Pathology (USA). This book aims to supplement and complement this trend by acting as an educative and practical tool for both trainees and consultants. It provides an easily understood and memorized framework for standardized histopathology reports in surgical cancer. It notes the gross description, histological classification, tumour differentiation, extent of local tumour spread, involvement of lymphovascular channels, lymph nodes and excision margins of the common carcinomas and summarizes non-carcinomatous malignancies. It incorporates the fifth edition TNM classification of cancer spread, comments on any associated pathology and gives diagnostic clues and prognostic criteria. The staging information is supplemented visually by line diagrams. It emphasizes those features of a particular cancer that are relevant to clinical management and prognosis. It aims to give the reader a more systematic and analytical approach to the description of surgical pathology specimens, resulting in reports that are consistent and inclusive of the data necessary for the surgical and oncological management of patients. Its format acts as an aide-memoire for routine reporting of the common cancers, but it also lists diagnostic options and summary features of rarer cancers as a pointer to their diagnosis and consultation of specialist texts, as listed in the Bibliography. Reports inclusive of the data herein should also facilitate demographic, research, quality control and audit procedures. I hope that you find the information in this book to be interesting, relevant and of practical use.

The author gratefully acknowledges the use of illustrations from Hermanek P, Hutter RVP, Sobin LH, Wagner G, Wittekind Ch (eds). TNM Atlas: Illustrated Guide to the TNM/pTNM Classification of Malignant Tumours, 4th edn. Springer. Berlin Heidelberg New York 1997.

I would like to express my grateful appreciation to Nick Mowat, Phil Bishop, Nick Wilson and the staff at Springer, my colleagues at the Belfast City Hospital Histopathology Laboratory and Mrs Debbie Green and Miss Kim Turkington for their secretarial expertise. Thanks also to my wife Alison and our girls, Katie, Rebecca and Amy, who often kept quiet when "Mr Grumpy" wanted them to.

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Contents

Introduction

Histopathology reports on surgical cancer specimens are becoming increasingly complex for many reasons. With closer clinicopathological correlation and the use of novel immunocytochemical and molecular techniques, new entities and classifications of tumour emerge that are linked to prognosis and response to various treatment modalities. Increasingly the surgical oncologist wants tissue biopsy proof of cancer diagnoses so that patients may be recruited to suitable treatment protocols. No longer is it sufficient to simply say what it is—this must now be qualified by assessment of prognostic indicators such as tumour grade, extent of spread, relationship to primary excision margins, lymph node and vascular spread. Accurate classification and information on tumour stage and prognosis requires increased time and detail on surgical pathology dissection and reporting. These necessary but stringent demands are met by diagnostic surgical pathologists with varying degrees of success and standards of reporting. For example, an audit of colorectal cancer pathology reports in one National Health Service region of the United Kingdom showed that only 78% of colonic cancer reports and 47% of rectal cancer reports met previously agreed criteria in providing the prognostically important information.

From this has arisen a trend towards set format reports or minimum datasets for the common cancers. In the United Kingdom this is sponsored by the Royal College of Pathologists allied to other interested parties, such as the Association of Clinical Pathologists and the UK Association of Cancer Registries. They do not work in isolation but in cooperation with other bodies specifically active in individual cancer types, e.g. breast cancer: NHS Breast Screening Programme, European Commission Working Group on Breast Screening Pathology and the British Breast Group. These new standards mirror changes in the organization and provision of cancer services in the United Kingdom reflected in the Calman–Hine Report "A Policy Framework for Commissioning Cancer Services". The success of this approach is measured by ongoing dataset revision and second cycle of publication (http://www.rcpath.org/index.asp?pageID=254). Similar standards for pathologists are also set in the United States by the Association of Directors of Anatomic and Surgical Pathology (http://www.panix.com/~adasp/tumor.htm and http://www.panix.com/~adasp/checklist%20page.htm) and published reg-

ularly in the journal *Human Pathology*. Parallel initiatives have been published in *Archives of Pathology and Laboratory Medicine* by the College of American Pathologists (http://www.cap.org/apps/docs/cancer_protocols/protocols_index.html).

From the pathologist's point of view standard reports act as an important aide-memoire for the inclusion of necessary data and audit shows that quality standards of information increase accordingly. Also, once the pathologist is familiarized with them, such reports are relatively time-efficient to dictate and transcribe. The clinician (surgeon or oncologist) can extract from them the relevant data with ease and cancer registries can be facilitated—supplemented by automated download if the database is suitably computerized.

The approach taken herein is aimed at fostering the use of standard format reports in surgical cancer. The headings used are common to all cancers, and can be preset onto a computer field or, if this is not available, easily memorized, dictated and typed in a listed format. The end product is concise, clear and relevant to patient management. The format is:

1. Gross description
   Specimen: description
   Tumour:
      Site
      Size
      Appearance
      Edge
2. Histological type
3. Differentiation/grade
4. Extent of local tumour spread
5. Lymphovascular invasion
6. Lymph nodes
7. Excision margins
8. Other pathology
9. Other malignancy

These criteria are chosen for the following reasons:

1. GROSS DESCRIPTION

Specimen

Specimen type; biopsy or resection. Full standard format reports are most relevant to resection specimens although the principles and abridged forms are applicable to biopsies. Sometimes a resection is more conveniently reported as free text, or in standard format but requiring clarification in the further comments section. If dictated as free text, care must be taken to include the standard diagnostic and prognostic parameters. Biopsy reports should at least comment on the following (if the data are available): tumour point of origin, type of cancer, differentiation or grade, extent of mucosal or submucosal spread, adjacent dysplasia or carci-

noma in situ and involvement of lymphovascular channels. The proportion of tissue involved by tumour can be useful, e.g. prostate cancer. It is important epidemiologically that cancer registries can distinguish between biopsy and resection specimens to avoid duplication of statistical data leading to overestimates of cancer incidence and prevalence. This can be achieved by unique patient identification and careful indexing of SNOMED T (topography) and P (procedure) codes. This also facilitates audit of biopsy and resection-proven cancer numbers and correlation with other techniques such as exfoliative or fine needle aspiration cytology, radiological imaging and serum marker levels (e.g. prostate specific antigen, PSA).

Specimen type also has implications for excision margins and clinical adjuvant treatment and follow-up, e.g. breast-sparing excision biopsy vs. mastectomy, diathermy snare polypectomy vs colonic resection.

Specimen weight and size. This may also be an indicator of the underlying pathology, e.g. primary adrenal cortical lesions >50 g are usually carcinoma rather than adenoma, and abundant vesicular uterine curettings up to 100 g suggest complete hydatidiform mole with subsequent potential for persistent trophoblastic disease and choriocarcinoma.

Tumour

Site

Location of tumour within the mucous membrane or wall can often give clues as to its nature. Mucous membrane lesions are often primary and epithelial or lymphoid in character. Mural lesions may be primary and mesenchymal or, similar to serosal disease, secondary and extrinsic. Site dictates which adjacent tissues are involved by direct spread (e.g. cervix carcinoma–ureter) and can indicate variable tumour differentiation and prognosis within a given structure (e.g. adenocarcinoma of the hilum vs. the distal third of the extrahepatic bile ducts). It can also be used as an audit tool to monitor resection rates as in anterior resection vs. abdominoperineal resection for rectal carcinoma. It can influence the diagnosis, e.g. epiphyseal vs. diaphyseal bone tumours, renal pelvis (transitional cell) carcinoma vs. renal cortical (clear cell) carcinoma. Laterality (right or left) is obviously extremely important in patient management. Some cancers also have a tendency for multifocal growth, e.g. transitional cell carcinoma of the urinary tract or thyroid papillary carcinoma.

Size

Size influences the diagnosis (gastrointestinal stromal tumours >5 cm are more likely to be malignant) and the prognosis (renal cell carcinoma: ≤7 cm = pT1, >7 cm = pT2; sarcoma: prognosis relates to tumour grade, size and adequacy of excision; breast carcinoma: Nottingham Prognostic Index = 0.2 × size (cm) + grade + lymph node stage). Gross measurements should ideally be made on the fresh tissue and checked against

the histological slide, allowing for tissue shrinkage with fixation and processing (e.g. to 30% for oesophageal resections). Small measurements are done with a dome magnifier, the stage micrometer or an eyepiece graticule. Guidelines are given (National Health Service Breast Screening Programme) to distinguish between size of invasive tumour from whole size (+ in-situ change) tumour measurements and a radiological performance indicator is the percentage yield of invasive tumours <1 cm in diameter.

Appearance

Luminal and polypoid

— oesophageal spindle cell carcinoma.
— uterine malignant mixed mesodermal tumour (carcinosarcoma).
— multiple lymphomatous polyposis or familial adenomatous polyposis coli.

Nodular

— carcinoid tumour of bronchus.
— malignant melanoma.

Sessile/plaque

— early gastrointestinal carcinoma (stomach, oesophagus, colorectum).
— lymphoma of gut.
— high-grade bladder carcinoma.

Ulcerated

— usual carcinoma morphology.

Fleshy

— malignant lymphoma.

Pigmented

— malignant melanoma.

Haemorrhagic

— choriocarcinoma (gestational or testicular).

Cystic

— ovarian carcinoma.
— renal carcinoma.
— thyroid papillary carcinoma.
— secondary squamous carcinoma of head and neck.

Edge

Circumscribed—mucinous carcinoma, medullary carcinoma and phyllodes tumour of breast, pancreatic endocrine tumours, some gut cancers.
Irregular—infiltrating carcinoma.

2. HISTOLOGICAL TYPE

For the most part this mirrors the World Health Organization (WHO) International Classification of Tumours, but draws on other classifications where appropriate, e.g. REAL—Revised European American Lymphoma classification—and the Heidelberg classification of renal carcinoma. The classifications have also been partially edited to reflect those diagnoses that are more commonly encountered or discussed as differential diagnoses.

Histological type influences:

1. Prognosis—breast carcinoma
   - — excellent: tubular, cribriform, mucinous.
   - — good: tubular mixed, alveolar lobular.
   - — intermediate: classical lobular, invasive papillary, medullary.
   - — poor: ductal (no special type), mixed ductal and lobular, solid lobular.
2. Management—lung carcinoma
   - — non-small cell carcinoma: surgery ± radiotherapy depending on stage.
   - — small cell carcinoma: chemo-/radiotherapy.
3. Tumour distribution
   - — thyroid papillary carcinoma: potentially multifocal.
   - — ovarian epithelial borderline tumours: bilaterality, peritoneal implants, pseudomyxoma peritonei, appendiceal neoplasia.
4. Associated conditions
   - — thyroid medullary carcinoma: multiple endocrine neoplasia syndromes (MEN).
   - — duodenal periampullary carcinoma: familial adenomatous polyposis coli.

3. DIFFERENTIATION/GRADE

Three-tier systems (well/moderate/poor differentiation or Grade 1/2/3, bladder carcinoma WHO I/II/III) have traditionally been used based on subjective assessment of similarity to the ancestral tissue of origin (e.g. keratinization and intercellular bridges in squamous carcinoma and tumour gland formation in adenocarcinoma), cellular pleomorphism,[1] mitoses[2] and

[1]Cellular pleomorphism: this largely relates to nuclear alterations in size, shape, polarity, chromasia, crowding and nucleolar prominence. Cytoplasmic differentiation may also be taken into account (e.g. breast carcinoma—tubule formation).

[2]Mitoses: The assessment of mitotic activity either as a stand-alone mitotic activity index or as part of a grading system is a strong prognostic factor as in breast carcinoma. However, care must be taken: (a) delayed fixation may significantly alter numbers of mitoses but also makes them more difficult to identify; (b) hyperchromatic, pyknotic, apoptotic bodies should be ignored and only clearly defined mitotic figures counted. Strict criteria should be used such as absence of the nuclear membrane and clear hairy extension of nuclear material ± increased basophilia of the cell cytoplasm; (c) counts should be related to a fixed field area against which various high-power microscope objectives can be calibrated. In general a ×40 objective is used.

necrosis.[3] This is strengthened when the individual criteria are formally evaluated and assimilated into a score that gives strong prognostic information (breast carcinoma, sarcoma). However, a subjective three-tier system is not advantageous when the majority of lesions fall into one category (e.g. colorectal carcinoma is predominantly moderately differentiated) and there is a lack of prognostic stratification. It is also compounded by poor reproducibility and tumour heterogeneity. This has resulted in emergence of two-tier systems to identify prognostically adverse cancers (poorly differentiated vs. others in colorectal carcinoma; low-grade/high-grade in non-Hodgkin's lymphoma and soft tissue sarcoma). In addition, specific grading systems exist, e.g. Fuhrman nuclear grade in renal cell carcinoma, the Bloom and Richardson grade in breast carcinoma and glandular/non-squamous morular components in uterine adenocarcinoma. Poor differentiation (G3) overlaps with and is sometimes combined with the undifferentiated (G4) category. Mixed differentiation with regard to tumour subtype and grade is relatively common. Carcinosarcoma/spindle cell carcinoma/sarcomatoid carcinoma represent carcinoma with spindle cell change and variable monophasic/biphasic/homologous/heterologous mesenchymal differentiation arising from malignant pluripotential stem cells.

4. EXTENT OF LOCAL TUMOUR SPREAD

Blocks

Due to tumour heterogeneity and variation in direct extension, multiple blocks of tumour and adjacent structures should be taken to ensure a representative sample. A useful general principle is one block per centimetre diameter of tumour mass with targeting of specific areas, e.g. solid foci in ovarian tumours, haemorrhagic foci in testicular tumours (choriocarcinoma).

Colorectal carcinoma: 4 or 5 blocks to show the tumour in relation to mucosa, wall, serosa and mesentery.

Thyroid nodule: 8 to 10 blocks including the capsule to distinguish follicular adenoma from minimally invasive follicular carcinoma.

Ovarian tumours: 1 block/centimetre diameter to account for the spectrum of benign, borderline and malignant changes in one lesion, particularly mucinous tumours.

Border

Pushing/infiltrative.

Lymphocytic reaction

Prominent/sparse.

Carcinomas with a pushing border and prominent lymphocytic reaction are regarded as having a better prognosis than those with a diffusely irregular infiltrating margin and sparse lymphocytic reaction, e.g. colorectal carcinoma, head and neck carcinoma, malignant melanoma, medullary carcinoma of breast, advanced gastric carcinoma.

[3]Tumour necrosis: apoptotic (single cell) or coagulative (confluent with pyknotic nuclear material in eosinophilic debris).

Perineural spread
Carcinoma prostate, gall bladder and extrahepatic bile duct, pancreas and adenoid cystic carcinoma. In prostatic cancer there is some evidence that perineural invasion relates to the presence of extracapsular spread of disease and in other cancers it increases the likelihood of local recurrence.

Breslow depth/Clark level
Malignant melanoma. Direct linear measurement (mm) and anatomical level of invasion of the vertical component are strong prognostic indicators.

TNM (Tumour Nodes Metastases) classification
The TNM classification is an international gold standard for the assessment of spread of cancer and the revised 6th edition has been published by the UICC (International Union Against Cancer) taking into account new prognostic information, investigations and treatments. The system has evolved over 50 years as a tool for the careful collection of accurate data pertaining to cancer spread which can then be consistently related to planning of treatment, prognosis, evaluation of treatment and exchange of information between clinicians and centres. Virtues are that it translates into hard data some of the subjective language used in descriptive pathology reports and also encourages the pathologist to be more analytical in approach. It also improves pathologist-to-clinician communication. The post-surgical histopathological classification is designated pTNM and is based on pre-treatment, surgical and pathological information.

pT requires resection of the primary tumour or biopsy adequate for evaluation of the highest pT category or extent of local tumour spread

pN requires removal of lymph nodes sufficient to evaluate the absence of regional node metastasis (pN0) and also the highest pN category

pM requires microscopic examination of distant metastases which is often not available to the pathologist and therefore designated on clinical or radiological grounds. If available (e.g. a multidisciplinary meeting), the TNM categories can be stratified into clinical stage groupings which are used to select and evaluate therapy, e.g. carcinoma in situ is stage 0 while distant metastases is stage IV. However, for the most part the pathologist concentrates on pT and pN which gives reasonably precise data to estimate prognosis and calculate end results. Stage grouping is mostly based on the anatomical extent of disease, but for some tumour sites or entities other factors are included: histological type (thyroid), age (thyroid), grade (bone, soft tissue, prostate), tumour markers (testis) and risk factors (gestational trophoblastic tumour).

Multiple synchronous tumours (diagnosis within 2 months of each other): classify the tumour with the highest pT category and indicate the

number of tumours in brackets, e.g. pT2 (4). In simultaneous bilateral cancers of paired organs each tumour should be classified independently. Systemic or multicentric cancers potentially involving many discrete organs are categorized only once in any individual, e.g. malignant lymphoma, leukaemia, Kaposi's sarcoma and mesothelioma. If there is doubt about the assigned T, N or M category in a particular case then the lower (i.e. less advanced) category is chosen. Note that in practice the multidisciplinary meeting may choose to upgrade the category to ensure that the patient receives adequate therapy, particularly in younger and fit individuals. When size is a criterion for the pT category, it is a measurement of the actual unfixed invasive component. Adjacent in-situ change is not counted and if the fixed specimen shows a significant discrepancy with the clinical tumour measurement, the latter is chosen.

Direct spread into an adjacent organ is recorded in the pT classification and is not considered distant metastasis, whereas direct spread into a regional lymph node is considered in the pN category.

pT	primary tumour
pTX	primary tumour cannot be assessed histologically
pT0	no histological evidence of primary tumour
pTis	carcinoma in situ
pT1, pT2, pT3, pT4	increasing size and/or local extent of the primary tumour histologically
pN	regional lymph nodes
pNX	regional lymph nodes cannot be assessed histologically (either not present or less than the number recommended for a regional lymphadenectomy appropriate to the organ concerned)
pN0	no regional lymph node metastasis histologically
pN1, pN2, pN3	increasing involvement of regional lymph nodes histologically.

Main categories can be subdivided for further specificity, e.g. pT1a or pT1b to signify unifocality or multifocality.

Note than an X classification does not necessarily signify inadequate staging, e.g. known metastatic disease (pM1) supersedes the pN category, or pNX may arise because of a correct decision to treat by local excision, e.g. therapeutic polypectomy in the colorectum.

The TNM classification is applied to carcinoma only in the majority of tissues. Other qualifying malignant tumours are malignant mesothelioma, malignant melanoma, gestational trophoblastic tumours, germ cell tumours and retinoblastoma.

TNM optional descriptors

L lymphatic invasion
- LX cannot be assessed
- L0 not present
- L1 present.

V venous invasion
- VX cannot be assessed
- V0 not present
- V1 microscopic
- V2 macroscopic.

Note that lymphovascular invasion does not qualify as local spread of tumour in the pT classification (except liver and testis).

Prefix

y tumour is classified during or after initial multimodality therapy
r recurrent tumour, staged after a disease-free interval
a classification first determined at autopsy.

Suffix

m multiple primary tumours at a single site
mi nodal micrometastasis ≤2 mm.
i nodal isolated tumour cells (ITC) ≤0.2 mm
sn sentinel nodes
cy positive pleural or peritoneal washings, e.g. pM1 (cy +). An exception is primary ovarian carcinoma where cy + is part of the pT category.

Where appropriate, other internationally recognized staging systems are also given, e.g.

Malignant lymphoma	Ann Arbor
Gynaecological cancers	International Federation of Gynaecology and Obstetrics (FIGO)

5. LYMPHOVASCULAR INVASION (LVI)

Definition

LVI usually relates to microscopic tumour emboli within small thin-walled channels in which distinction between post-capillary venule and lymphatic channel is not possible—hence the general term LVI is used. It is important to identify an endothelial lining to differentiate from retraction space artefact, which often comprises a rounded aggregate of tumour sited centrally and free within a tissue space. Other helpful features of LVI are red blood cells, thrombosis, a point of attachment to the endothelium and a paravascular location. In difficult cases endothelial markers (Factor VIII antigen, CD34, CD31) may be helpful but, in general, adherence to strict morphological criteria is recommended.

Significance

There is controversy as to the significance of LVI, but in practice most pathologists view tumours with prominent LVI as those that are most likely to show longitudinal submucosal spread/satellite lesions and lymph node involvement. Extratumoral LVI is regarded as more significant than

intratumoral LVI and is most frequently encountered at the invasive edge of the tumour. LVI in tissue well away from the tumour is a strong marker of local and nodal recurrence in breast carcinoma, and is a criterion indicating the need for postoperative adjuvant therapy. When present in the overlying skin it denotes the specific clinicopathological entity of inflammatory breast carcinoma, which is staged pT4. LVI is a strong determinant of adjuvant chemotherapy in testicular germ cell tumours. LVI also forms part of the pT classification for testicular and liver tumours, and, if present in a distant organ (e.g. lymphangitis carcinomatosa of the lung in prostate tumour), it is classified as pM1.

Vascular involvement

Some tumours (hepatocellular carcinoma, renal cell carcinoma) have a propensity for vascular involvement and care should be taken to identify this on specimen dissection and microscopy as it also alters the tumour stage. Extramural vascular invasion is a significant adverse prognostic factor in colorectal carcinoma but can be difficult to define. Sometimes one is reliant on circumstantial evidence of a tumour-filled longitudinal structure with a wall partly formed of smooth muscle, lying at right angles to the muscularis propria and adjacent to an arteriole. Widowed arteries can be a useful indicator of venular involvement in a number of situations. The significance of vessel wall infiltration without luminal disease is uncertain, but probably indicates potential access to the circulation.

6. LYMPH NODES

As discussed above, the assessment of regional lymph nodes in a surgical cancer resection requires sufficient numbers to be able to comment on the absence of regional metastases and also the highest pN category, i.e. the total node yield and the number involved are important. In gastric carcinoma this means sampling and examining up to 15 regional nodes. Thus, node yields can be used to audit both care of dissection by the pathologist, adequacy of resection by the surgeon and the choice of operation, e.g. axillary node sampling vs. clearance. All nodes in the specimen should be sampled and, although ancillary techniques exist (e.g. xylene clearance, revealing solutions), there is no substitute for time spent at careful dissection with a preparedness to revisit the specimen after discussion at the multidisciplinary meeting. Care should be taken not to double-count the same node. Sometimes minimum target yields can be used—eight nodes will detect the vast majority of Dukes' C colorectal carcinomas. The pathologist should also remember to count those nodes in the histological slides that are immediately adjacent to the tumour, as they are sometimes ignored yet more likely to be involved.

What is a node?

— a lymphoid aggregate ≥1 mm diameter with an identifiable subcapsular sinus.
— direct extension of the primary tumour into lymph nodes is classified as a lymph node metastasis (TNM rule).

— a tumour nodule in the connective tissue of a lymph drainage area without histological evidence of residual lymph node is classified in the pN category as a regional lymph node metastasis if the nodule has the form and smooth contour of a lymph node (having first ensured that it does not represent tumour in a venule). A tumour nodule with an irregular contour is classified in the pT category, i.e. as discontinuous extension. It may also be classified as venous invasion (V classification), either microscopic (V1) or macroscopic (V2), as this is its likely origin.

Note that this differs from the 5th edition TNM classification, in which a connective tissue drainage area nodule <3 mm was designated as discontinuous extension and ≥3 mm as a nodal metastasis. Although this change probably more accurately reflects biological events, it has caused discussion in the UK with concerns over observer reproducibility of the TNM 6 rule and inconsistency with on-going international trials. The resolution of this issue awaits further studies.

When size is a criterion for pN classification, e.g. breast carcinoma, measurement is of the metastasis, not the entire node (TNM rule). Size is also the whole measurement of a conglomerate of involved lymph nodes, and includes perinodal tumour.

Micrometastases

The significance of nodal micrometastases ≤2 mm (designated (mi), e.g. pN1 (mi)) and isolated tumour cells (ITC) ≤0.2 mm (designated (i+), e.g. pN0 (i+)) demonstrated by immunohistochemistry is not resolved. In practical terms an accommodation within available resources must be made. Most busy general laboratories will submit small nodes (<5 mm) intact or bisected, and a mid-slice of larger ones. Additional slices may be processed as required if the histology warrants it. Sometimes there is circumstantial evidence of occult metastases, e.g. a granulomatous response that will promote the use of immunohistochemistry in the search for single cell spread. The prognostic significance of micrometastases has yet to be clarified for the majority of cancers, e.g. a search for micrometastases is advocated by some in breast and colorectal carcinoma but considered to be of equivocal significance in oesophageal carcinoma. This area needs further clarification from large international trials which examine clinical outcome related to the immunohistochemical and molecular (reverse transcriptase-polymerase chain reaction, RT-PCR) detection of minimal residual disease in lymph nodes and bone marrow samples considered tumour-negative on routine examination. Detection by non-morphological techniques such as flow cytometry or DNA analysis is designated (mol+), e.g. pN0 (mol+) or pM0 (mol+) in lymph node or bone marrow, respectively. In the interim, the rationale behind assigning (i+) and (mol+) to the pNO category is because they do not typically show evidence of metastatic activity, e.g. proliferation, stromal reaction or penetration of vascular or lymphatic sinus walls.

Limit node
The limit node is the nearest node(s) to the longitudinal and/or apical resection limits and suture ties. Some specimens, e.g. transverse colon, will have more than one and they should be identified as such.

Extracapsular spread
Extracapsular spread is an adverse prognostic sign and an indicator for potential local recurrence (bladder cancer), particularly if the spread is near to or impinges upon a resection margin, e.g. axillary clearance in breast carcinoma. Perinodal tumour is also included in measurement of metastasis maximum dimension.

7. EXCISION MARGINS

The clearance of excision margins has important implications for patient follow-up, adjuvant therapy and local recurrence of tumour. Positive resection margins in a breast cancer may mean further local excision, conversion to a total mastectomy and/or radiotherapy to the affected area. Measurements should be made on the gross specimen, checked against the histological slide and verified using the stage micrometer or eyepiece graticule. A very useful practical aid is a hand-held perspex dome magnifier that contains an in-built graduated linear scale. Painting of the margins by ink supplemented by labelling of the blocks is important. Paint adheres well to fresh specimens but also works on formalin-fixed tissue. India ink or alcian blue are commonly used. Commercially available multi-coloured inks are helpful, particularly if there are multiple margins as in breast carcinoma. The relevance of particular margins varies according to specimen and cancer type.

1. *Longitudinal margins*. Involvement can be by several mechanisms:
   (a) *Direct spread*. In rectal carcinoma the longitudinal margin in an anterior resection is considered satisfactory if the anastomosis is 2–3 cm beyond the macroscopic edge of the tumour, i.e. direct longitudinal spread is minimal. However, there may be involvement if the tumour is extensively infiltrative, poorly differentiated or of signet ring cell type, or shows prominent LVI. Appropriate limit blocks should be taken. In addition to the resection specimen limits, separate anastomotic rings are also usually submitted.
   (b) *Discontinuous spread.* In oesophageal and gastric carcinoma there is a propensity for discontinuous lymphovascular submucosal and mural spread, and margins should be checked microscopically even if some distance from the primary tumour.
   (c) *Multifocal spread*. In transitional cell carcinoma of the urinary tract, malignant lymphoma of the bowel and papillary carcinoma of the thyroid, potential multifocality must be borne in mind.
2. *Circumferential radial margin (CRM)*. An often ignored measurement, these margins are assuming increasing importance in relation to local recurrence and morbidity, e.g. mesorectal CRM and rectal carcinoma. It is recommended practice to measure how far the carcinoma has

spread beyond the organ wall and how far it is from the CRM. Other examples are: oesophageal carcinoma and the adventitial margin, cervical carcinoma and the parametrial margin, renal carcinoma and the perinephric fat/fascial margin. Lymph node metastasis at a CRM is also considered positive. The significance of some other examples is less well defined but comment should be made, e.g. the mesenteric edge in colonic carcinoma.

3. *Quadrant margins*. Examples are a skin ellipse for carcinoma or malignant melanoma. Usually the longitudinal axis margins are well clear and the nearest to the tumour are the transverse axis and deep aspects. It is important to check clearance not only of the infiltrating tumour but also adjacent field change, e.g. epidermal dysplasia or radial spread of a malignant melanoma. Actual measurement of margin clearance can be important in assessing the need for further local excision, e.g. malignant melanoma. An alternative technique is multiple serial transverse slices demonstrating the entirety of the transverse axis margins with the longitudinal axis tips also embedded in toto ("toast-racking").
4. *Serosa or peritoneum*. This is a visceral margin and breech of it allows carcinoma to access the abdominal and pelvic cavities. Its importance has been re-emphasized, as for example at the upper anterior aspect of the rectum where there is potential for peritoneal disease as well as local mesorectal recurrence posterolaterally. Standard practice may also involve measuring the distance from the invasive edge of the tumour to the serosa, e.g. uterine adenocarcinoma.

   Colonic carcinoma: serosa; prognostic distinction is made between carcinoma in a subserosal inflammatory reaction (pT3) and carcinoma being at and ulcerating the serosal surface (pT4).
5. *Multiple margins*. As in breast carcinoma (lateral/medial, superior/inferior, superficial/deep), this requires differential painting and block labelling, according to a previously agreed protocol for specimen orientation markers, e.g. surgical sutures. Alternatively, the surgeon may submit multiple site oriented shave margins marked as to their inner and outer (new in-vivo margin) aspects.
6. *Involvement*. Inadequate clearance of excision margins varies according to the tissues and tumours concerned:
   Breast carcinoma: invasive, <5 mm; in-situ (ductal), <10 mm
   Rectal carcinoma: mesorectum, ≤1 mm (either by direct extension or discontinuous in a node or lymphovascular channel).

TNM resection classification

R residual tumour
Rx presence of residual tumour cannot be assessed
R0 no residual tumour
R1 microscopic residual tumour (proven by tumour bed biopsy or cytology) and in effect if tumour involves (to within ≤1 mm) the resection margin
R2 macroscopic residual tumour.

Residual disease takes into consideration not only locoregional tumour but also any remaining distant metastases. It can also be applied following surgery, radiotherapy or chemotherapy, alone or in combination. For a number of tumour sites there are also semiquantitative histological regression grading systems applicable to post multimodal treatment.

8. OTHER PATHOLOGY

This heading reminds the pathologist to look for and comment on relevant predisposing and concurrent lesions, associated conditions and useful markers.

Some examples are:

— gastric carcinoma, incomplete (type IIb) intestinal metaplasia, gastric atrophy, dysplasia, synchronous MALToma, Helicobacter pylori.
— colorectal carcinoma, adenomatous polyps, familial adenomatous polyposis coli, periampullary carcinoma and duodenal adenoma.
— thyroid medullary carcinoma, multiple endocrine neoplasia (MEN) syndromes.
— hepatocellular carcinoma, hepatitis B/C infection, cirrhosis, Budd–Chiari syndrome, varices.

Other general comments are included such as diagnostic criteria, immunophenotype, prognostic indicators, clinical and treatment parameters. Local recurrence and survival rates are both specific to individual sources and broadly indicative of the data available in the Bibliography references.

9. OTHER MALIGNANCY

The TNM classification is targeted primarily at carcinoma but also includes malignant mesothelioma, malignant melanoma, gestational trophoblastic tumours, germ cell tumours and retinoblastoma. This section notes the commoner non-carcinomatous cancers such as uterine and gastrointestinal smooth muscle/stromal tumours, lymphoma/leukaemia and sarcoma. Summary diagnostic and prognostic criteria are given, where relevant.

Ancillary techniques

Various ancillary techniques can be useful in the histopathology of surgical cancer and should be employed as appropriate. Some of these are commented on at various points in the protocols, e.g. under sections 2. Histological type and 8. Other pathology.

Cytology

Fine needle aspiration cytology (FNAC) using 25–22-G needles has become the first-order investigation in many cancers due to its speed, cost-effectiveness, proficiency and convenience for both clinician and patient. It can not only provide specific inflammatory (e.g. Hashimoto's thyroiditis) and malignant diagnoses (e.g. thyroid papillary carcinoma) but can sort patients into various management groups: viz, inflammatory

and treat, benign and reassure, atypical and further investigation (by core/open biopsy or excision) or malignant with specific therapy (surgery, chemotherapy, radiotherapy). It can be used to refute or confirm recurrence in patients with a known previous diagnosis of malignancy and to monitor response to therapy or change in grade of disease. It provides a tissue diagnosis of cancer in patients unfit for more invasive investigations or when the lesion is relatively inaccessible, e.g. in the lung periphery, mediastinum, abdomen, pelvis and retroperitoneum. It must be integrated with the clinical features and investigations (serology, radiology) and can be complemented by other techniques, e.g. core biopsy. It potentially provides material for routine morphology, histochemical and immunohistochemical techniques, electron microscopy, cell culture and flow cytometry. The direct smear and cytospin preparations can be augmented by formalin-fixed paraffin-processed cell blocks of cell sediments and needle core fragments (mini-biopsies), which can combine good morphology (the cores providing a tissue pattern) and robust immunohistochemistry. It can be applied to many organs: salivary gland, thyroid gland, palpable lymphadenopathy, breast, skin, prostate, subcutaneous tissues and deep connective tissues, although in some cases, e.g. breast cancer, a lack of locally available cytopathological expertise has resulted in a trend back towards core needle biopsy. Radiologically guided FNAC is useful for non-central respiratory cancers and tumours in the mediastinum, liver, pancreas, kidney, retroperitoneum, abdomen and pelvis. Endoscopic FNAC is also being used more frequently, e.g. transbronchial, transrectal, transduodenal and transgastric/transoesophageal for lymph node staging or tumours covered by intact mucosa. Body cavity fluid cytology (both aspirates of free pleural, pericardial and peritoneal fluid and peritoneal/pelvic washings) continues to play an active role in the diagnosis, staging and monitoring of cancer. Yield of information is maximized by a combination of morphology and immunohistochemistry on direct smear/cytospin preparations (using air-dried Giemsa and wet-fixed Papanicolaou/H&E stains) and cell blocks (cell sediments and fragments).

Exfoliative cytology along with cytological brushings and washings is also pivotal in the assessment of various cancers, e.g. lung cancer, where the information obtained is complementary to that derived from direct biopsy and aspiration cytology. It can provide diagnostic cells not present in the biopsy specimen (for reasons of sampling error, tumour type or accessibility), correlate with it or allow subtyping that is otherwise obscured in artefacted biopsy material. Common sites of application are bronchus, mouth, oesophagus, stomach, bile duct, large intestine, bladder, renal pelvis and ureter.

Liquid-based preparations with good morphology and preservation of immunogenicity are increasingly complementing or replacing traditional cytological methods.

Frozen sections

There has been a dramatic reduction in breast pathology due to the triple approach of clinical, radiological and cytological examination (supple-

mented by wide core needle biopsy) resulting in preoperative diagnosis and appropriate planning of treatment. Frozen section is contraindicated in impalpable screen-detected lesions. Other uses are:

— check excision of parathyroid glands vs. thyroid nodules or lymph nodes in hyperparathyroidism.
— operative margins in gastric carcinoma, partial hepatectomy, head and neck and urinary cancers.
— cancer vs. inflammatory lesions at laparotomy.
— lymph node metastases in head and neck, urological, and gynaecological cancers prior to radical dissection.
— Mohs' micrographical surgery in resection of basal cell carcinoma of the face.
— frozen sections should be used sparingly due to problems of interpretation and sampling in the following cancers: malignant lymphoma, ovarian carcinoma, minimally invasive thyroid carcinoma, pancreas and extrahepatic bile duct carcinoma.

Histochemical stains

Histochemical stains are appropriately mentioned and can be valuable, examples being: PAS ± diastase or mucicarmine for adenocarcinomatous differentiation, PAS-positive inclusion bodies in malignant rhabdoid tumours and alveolar soft part sarcoma, PAS-positive glycogen in renal cell carcinoma.

Immunohistochemistry

Immunohistochemistry has become the surgical pathologist's "second H&E" and is invaluable in assessing tumour type, prognosis and potential response to treatment.

Tumour type

— further detail is given in their respective chapters but typical cancer type immunoprofiles are given in Table A.
— select antibody panels are also of use in differential diagnosis in a number of circumstances (Table B).
— the cytokeratin subtypes CK7 and CK20 have an important role to play in tumour characterization (Table C).

Prognosis

— Her-2, p53 oncogene expression, Ki-67 (MIB-1) proliferation index.

Potential treatment response

— oestrogen/androgen expression and hormonal response in breast (e.g. tamoxifen) and prostate cancer.
— Her-2 expression and Herceptin (trastuzumab) therapy in breast cancer.
— CD20 expression and Rituximab therapy in non-Hodgkin's malignant lymphoma.
— CD117 expression and imatinib (Glivec STI 571) therapy in GISTs.

Table A Immunoprofile of cancer types

System	Tumour/condition	Marker panel
Head and neck	Salivary gland tumours	Epithelium: AE1/AE3 and myoepithelium: S100, Sm actin, calponin, CK 5/6
	Thyroid gland carcinoma	Papillary and follicular: thyroglobulin, TTF-1, CK19, galectin 3. Medullary: calcitonin, CEA, chromogranin
Gastrointestinal	Oesophageal carcinoma	Squamous cell: AE1/AE3 Adenocarcinoma: CAM5.2, CK7, ± CK20 (>50%)
	Barrett's oesophagus	Villin, cyclin D1, p53, Ki-67
	Gastric adenocarcinoma	CEA, EMA, CK7, ± CK20 (> 50%), CDX-2
	Small bowel adenocarcinoma	CEA, EMA, CK20, ± CK7 (50%)
	Colorectal adenocarcinoma	CEA, EMA, CK20, CDX-2, ± CK7 (5–10% particularly with poor differentiation or MSI-H)
	Hepatocellular carcinoma	AFP, Hep Par1, CEA (polyclonal/canalicular), CD10, CAM5.2, CK8, CK18
	Pancreaticobiliary carcinoma	CEA, CA19-9, CA125, CK7, CK19, ± CK20, CDX-2
	Gastrointestinal stromal tumours	CD117, CD34, vimentin, Ki-67, ± Sm actin, desmin, S100, protein kinase c theta
	Neuroendocrine carcinoids	Chromogranin, synaptophysin, CD56, ± CAM5.2, Ki-67, gastrin, insulin, glucagon
Respiratory	Small cell carcinoma	CAM5.2 (paranuclear dot), CD56, synaptophysin, chromogranin, TTF-1, Ki-67
	Non-small cell carcinoma	Adenocarcinoma: CAM5.2, Ber EP4, CEA, CK7, TTF-1, PE10, CD15, MOC 31 No specific type: AE1/AE3, CK5/6, 34βE12
	Malignant mesothelioma	Positive: CAM 5.2, AE1/AE3, CK5/6, CK7, calretinin, WT1, thrombomodulin, HBME1, p53, EMA Negative: CEA, BerEP4, CD15, MOC 31
Gynaecological	Ovarian carcinoma	Serous: CK7, CA125, WT1 Mucinous/endometrioid: CEA, CK7, ± CK20, CDX-2
	Sex cord stromal	Inhibin, vimentin, calretinin, CD99, ± CAM5.2, AE1/AE3, EMA, Ki-67
	Uterus, mesenchymal	Leiomyomatous: desmin, h-caldesmon, oxytocin, Sm actin, ± CD10, Ki-67 Stromal: CD10, Ki-67, ± desmin, h-caldesmon, Sm actin
	Endometrial carcinoma	ER, vimentin, CAM5.2, AE1/AE3, CK7, ± CK20, CD10, p53 (serous)
	Cervix—CGIN	Ki-67, p16, bcl-2
	Cervical adenocarcinoma	CEA, CK7, ± CK20 (ER/vimentin negative), p16
	Hydatidiform mole	p57 kip2 in partial/complete (present/absent)

Genitourinary	Renal clear cell carcinoma	CAM5.2, AE1/AE3, CD10, EMA, vimentin, CD15, RCC ab
	Renal papillary carcinoma	As above but also CK7, Ber EP4
	Renal chromophobe carcinoma	As above including CK7, Ber EP4, E-cadherin, MOC 31 (and decreased CD10, vimentin, RCC ab)
	Transitional cell carcinoma	34βE12, AE1/AE3, CK7, CK20, p53, uroplakin
	Prostate carcinoma	PSA (polyclonal), PSAP, AMACR (P504S) but 34βE12, p63 basal cell negative
	Testicular germ cell tumour	Seminoma: PLAP, CD117, HCG, inhibin (syncytiotrophoblast giant cells) Embryonal carcinoma: CAM5.2, CD30, ± PLAP Yolk sac tumour: CAM5.2, AFP Choriocarcinoma: HCG, CK7 (cytotrophoblast)
Breast	Breast carcinoma	ER, PR, Her-2/neu, CK7. Also Sm actin, CK5/6, CK14, CK8/18, E-cadherin (see Chapter 22)
Soft tissue	Spindle cell sarcoma	Vimentin, CD34, Sm actin, desmin, h-caldesmon, CAM5.2, AE1/AE3, EMA, S100, HHV8
	Small round blue cell tumours	CD45, tdt, S100, CD99, Fli1, desmin, myogenin, WT1, NB84, CAM5.2, CD56, CK20
	Adrenal carcinoma	Inhibin, melan-A, synaptophysin (cytokeratin, EMA, CEA negative)
	Phaeochromocytoma	Chromogranin, S100 sustentacular cells (cytokeratin negative)
Skin	Malignant melanoma	S100, melan-A, HMB 45, Ki-67
	Merkel cell carcinoma	CD56, CK20, CAM5.2
Haematopoietic	Malignant lymphomas	CD45, CD20, CD3 and CD4, CD5, CD8, CD10, CD15, CD21, CD23, CD30, CD56, CD57, κ and λ, cyclin D1, bcl-2, bcl-6, bcl-10, ALK, Ki-67, LMP1, EBER, granzyme B, myeloperoxidase, mum 1

Sm actin, smooth muscle actin; TTF-1, thyroid transcription factor; CK, cytokeratins: specific (e.g. CK7, 20) or cocktails: CAM5.2, CKs 8, 18, 19; 34βE12, CKs 1, 5, 10,14; AE1/AE3, CKs 10, 15, 16, 19/1-8; AFP, alphafetoprotein; HCG, human chorionic gonadotrophin; PLAP, placental alkaline phosphatase; Hep Par1, hepatocyte antibody; RCC ab, renal cell carcinoma antibody; CD56, neural cell adhesion molecule (NCAM); Ki-67, MIB 1; ER, oestrogen receptor; PR, progesterone receptor; PSA, prostate specific antigen; PSAP, prostate specific acid phosphatase; AMACR, alpha-methylacyl co-enzyme A racemase; tdt, terminal deooxynucleotidyltransferase; ALK, anaplastic lymphoma kinase; LMP1, latent membrane protein (EBV); EBER, EBV encoded RNA (in-situ hybridization); MSI-H, high level of microsatellite instability.

Adapted from McManus DT. Miscellaneous specimens. In Derek C Allen, R Iain Cameron (eds). Histopathology Specimens. Clinical, Pathological and Laboratory Aspects. Springer, London 2004

Queries about immunohistochemical staining may be answered at Immuno Query (http://www.ipox.org/login.cfm).

Table B Select antibody panels in differential diagnosis

Differential diagnosis	Antibody panel
Poorly differentiated tumour	
• carcinoma/melanoma/lymphoma/germ cell tumour/sarcoma (epithelioid variants)	CAM5.2, AE1/AE3, S100, melan-A, HMB-45, CD45, CD30, ALK, PLAP, CD117, desmin, CD34
Mesothelioma/pulmonary adenocarcinoma	AE1/AE3, CK5/6, calretinin, thrombomodulin, EMA, CEA, Ber EP4, MOC 31, TTF-1
Small round cell tumour	
• small cell carcinoma/Merkel cell carcinoma/lymphoma/leukaemia/Ewing's: PNET/rhabdomyosarcoma/neuroblastoma/intra-abdominal desmoplastic small cell	CAM 5.2, CD56, CK20, CD45, tdt, CD99, desmin, myogenin, synaptophysin, WT1, Ki-67
Bladder/prostate carcinoma	CK7, CK20, 34βE12, PSA, PSAP
Renal carcinoma/adrenal cortical neoplasm/phaeochromocytoma	CAM5.2, AE1/AE3, CD10, EMA, RCC ab, inhibin, melan-A, synaptophysin, S100, chromogranin
Hepatocellular carcinoma/cholangiocarcinoma/metastatic colorectal carcinoma	CAM5.2, AE1/AE3, AFP, Her Par 1, CEA (polyclonal/canalicular), CD10, CK7, CK20, CDX-2
Paget's disease of nipple/melanoma/Bowen's disease	CAM5.2, AE1/AE3, EMA, CK7, Her-2, S100, melan-A, (CK20 for anovulval Paget's)
Metastatic adenocarcinoma of unknown primary site: site indicative antibodies	Thyroglobulin, TTF-1: thyroid carcinoma and lung adenocarcinoma CEA, calcitonin: medullary carcinoma thyroid PSA (polyclonal), PSAP: prostate carcinoma CDX-2: gastrointestinal carcinoma CA125: ovary and sometimes pancreas, breast carcinoma GCDFP-15, ER, PR: breast carcinoma CA19-9: pancreas, upper gastrointestinal carcinoma PLAP, CD117, CD30: germ cell tumour AFP, Hep Par 1, CEA (polyclonal/canalicular): hepatocellular carcinoma RCC ab, CD10: renal cell carcinoma CK7, CK20: see Table C

Table C CK7, CK20 tumour expression

Immunoprofile	Carcinoma
CK7 + CK20 +	Gastric adenocarcinoma Pancreatic adenocarcinoma Transitional cell carcinoma Ovarian mucinous adenocarcinoma
CK7 + CK20 –	Lung adenocarcinoma Breast adenocarcinoma Ovarian serous and endometrioid adenocarcinoma Endometrial/endocervical adenocarcinoma (usually CK20 negative) Mesothelioma
CK7 – CK20 +	Colorectal adenocarcinoma
CK7 – CK20 –	Prostate adenocarcinoma Renal clear cell adenocarcinoma Hepatocellular carcinoma Lung carcinoma (non-adenocarcinoma types)

Antibodies should not be used in isolation but a panel employed with positive and negative in-built and external controls. This is due to a spectrum of co-expression seen with a number of antibodies, e.g. EMA (carcinoma, plasmacytoma, Hodgkin's disease and anaplastic large cell lymphoma) and CD15 (Hodgkin's disease and lung adenocarcinoma). Interpretation should also be closely correlated with the morphology. The above are only part of a rapidly enlarging spectrum of new generation, robust antibodies that can be used with formalin-fixed paraffin-embedded tissues and show enhanced demonstration of expression by heat-mediated antigen retrieval techniques such as microwaving and pressure cooking, and highly sensitive polymer-based detection systems. It is important to determine that the immunopositive reaction is in an appropriate location (e.g. membrane staining for Her-2/neu, nuclear staining for ER, TTF-1), is not simply related to entrapped normal tissues (e.g. infiltration of skeletal muscle fibres), and is of appropriate staining intensity. In some circumstances the number of positive cells is important, e.g. Ki-67.

Electron microscopy

Electron microscopy has a diagnostic role to play where morphology and immunochemistry are inconclusive. Specific features can be sought in:

— carcinoma (tight junctions, short microvilli, secretory vacuoles, intermediate filaments).
— melanoma (pre-/melanosomes).
— vascular tumours (intra-cytoplasmic lumina, Weibel-Palade bodies).
— neuroendocrine carcinoma (neurosecretory granules).
— mesothelioma (long microvilli).
— smooth muscle/myofibroblastic tumours (longitudinal myofilaments with focal dense bodies).

— rhabdomyosarcoma (basal lamina, sarcomere Z line formation).
— perineural/meningeal lesions (elaborate complex cytoplasmic processes).

Molecular and chromosomal studies

Evolving areas of diagnostic use of molecular and chromosomal studies are clonal immunoglobulin heavy chain and T-cell receptor gene rearrangements in the confirmation of lymphoma, and the characterization of various cancers (particularly lymphoma, sarcoma and some carcinomas, e.g. renal) by specific chromosomal changes. Gene rearrangement studies can be carried out on formalin-fixed paraffin-embedded material but fresh tissue put into suitable transport medium is required for chromosomal analysis—although RT-PCR methods are being developed for paraffin material. Genotypic subtypes of various malignancies, e.g. rhabdomyosarcoma, have been defined with differing clinical presentation, prognosis and response to therapy. Some examples are:

follicle centre lymphoma, follicular	t(14;18)
mantle cell lymphoma	t(11;14)
synovial sarcoma	t(X:18)(p11.2;q11.2)
myxoid liposarcoma	t(12;16)(q13;p11)

In-situ hybridization techniques may be used to detect viral nucleic acid (e.g. EBV in post transplant lymphoproliferative disorders, HPV subtyping in cervical biopsies), lymphoid clonality (κ, λ light chain mRNA) and karyotypic abnormalities such as Her-2/neu amplication in breast cancer and n-myc in neuroblastoma.

Quantitative methods

There is an expanding literature regarding the use of quantitative methods as diagnostic aids. These include stereology, morphometry, automated image analysis, DNA cytophotometry and flow cytometry. In general, adverse prognosis is related to alterations in tumour cell nuclear size, shape, chromasia, texture, loss of polarity, mitotic activity index, proliferation index (Ki-67 or S-phase fraction on flow cytometry), DNA aneuploidy and spatial density. Most of these techniques show good correlation with carefully assessed basic histopathological criteria and, rather than replacing the pathologist and microscope, serve to emphasize the importance of various parameters and sound morphological technique. Areas of incorporation into pathological practice are:

— morphometric measurement of Breslow depth of melanoma invasion, osteoid seams in osteomalacia and muscle fibre type and diameter in myopathy.
— mitotic activity index in breast carcinoma.
— DNA ploidy in partial vs. complete hydatidiform mole.

With the advent of more sophisticated computers and machine-driven technology, artificial intelligence and automated tissue analysis are being explored:

— automated cervical cytology.
— inference and neural networks in prostatic cancer and colonic polyps.
— Bayesian belief networks and decision support systems in breast cytology.
— MACs (malignancy associated changes) in prostate cancer based on alterations in nuclear texture.
— bioinformatics facilitates analysis of gene and tissue microarrays used to test the level of expression for multiple genes in relatively few samples, and the staining pattern of relatively few markers on a large number of samples, respectively. This allows more standardized scoring of current prognostic markers on samples from multiple patients, and also leads to the discovery of new prognostic cancer biomarkers.

This whole area is rapidly developing and evolving, and it remains to be resolved as to which facets will eventually be incorporated into routine practice.

Error, audit, quality assurance, clinical governance and digitized microscopy

Errors in a subjective discipline such as diagnostic pathology are inevitable, but rates are surprisingly low (1–2%). Whether cognitive (oversight or interpretational) or operative (non-analytical), they may be purely academic (e.g. a difference in nomenclature) or clinically significant (e.g. a false-positive diagnosis of cancer). Any surgical pathologist hopes to avoid the latter and the potential consequences for the patient. Errors are discovered by various routes: inconsistency in clinical outcome with individual case review, review at regular multidisciplinary cancer meetings, topic related audit, systematic selective surgical case review, or prospective in-house or external case referral for opinion. Clinical governance defines standards of care with open acknowledgement, communication and correction of errors. Professionals are encouraged to quality control, sometimes double report, and check their work in a team context supporting colleagues and identify any indicators of underperformance. In the UK the Royal College of Pathologists Professional Standards Unit publishes protocols and advises on issues of professional performance with the capacity to investigate and recommend remedial action in individual cases. Consequently, most pathologists adopt several strategies to maintain standards, including participation in continuing professional development (CPD) and external quality assurance (EQA) schemes. CPD entails attendance at local, national and international conferences and seminars, journal reading and other educational activities relevant to the pathologist's practice with reinforcement of strengths and identification of knowledge gaps. This approach is inherent to annual appraisal (and potentially revalidation), which should be consolidative and developmental in nature. EQA schemes are general or specialist in type with precirculation of slides and clinical clues. The pathologist submits diagnostic answers which are marked in comparison with the participants' consensus diagnoses. Results are confidential to the patho-

logist but an individual with repeated outlying marks will be flagged up to the scheme co-ordinator so that appropriate advice can be given. Definition of what constitutes a specialist pathologist is complex but at least involves spending a significant amount of professional time practising in the relevant area and participation in an appropriate EQA scheme. Pragmatically, experience tells who to send the referral case to and just "who can do the business". The ever-improving technology of digitized virtual microscopy will develop a role as an alternative to slide circulation in EQA schemes and case referral to experts, as potentially will telepathology for live remote diagnostic reporting to supplement its current use as a tool to facilitate cross site multidisciplinary meetings. Automated immunocytochemistry, multiblocks and microarrays will augment morphology by assessment of multiple prognostic markers. Thus the way ahead is charted for the surgical pathologist, and in all of this there may well still be no substitute for showing a slide around to colleagues whose opinion you value.

Gastrointestinal Cancer

- Oesophageal Carcinoma
- Gastric Carcinoma
- Ampulla of Vater and Head of Pancreas Carcinoma
- Small Intestinal Carcinoma
- Colorectal Carcinoma
- Vermiform Appendix Tumours
- Anal Canal Carcinoma (with comments on pelvic exenteration)
- Gall Bladder Carcinoma
- Extrahepatic Bile Duct Carcinoma
- Liver Carcinoma

1

Oesophageal Carcinoma

1. GROSS DESCRIPTION

Specimen

— oesophageal cancer usually presents with progressive dysphagia initially for solids and ultimately liquids. Investigation is by endoscopy and biopsy, and chest X-ray to detect any enlargement of the heart, mediastinal lymph nodes or lung lesion that may be causing extrinsic compression. For biopsy-proven cancer, staging for local and distant disease includes endoluminal ultrasound (tumour depth and nodal spread), computed tomographic (CT) scan chest and abdomen and positron emission tomographic (PET) scan. Treatment may be palliative (radiotherapy, stent) in bulky high-stage disease, or curative in intent with earlier lesions. The latter may involve neoadjuvant radio-/chemotherapy to downstage the tumour and then surgery, or surgery alone. Choice of operative procedure depends on the general health of the patient, the tumour site and extent, the choice of planned oesophageal substitute (stomach, jejunum, colon) and preference of the surgeon. Ideally, longitudinal clearance margins of 5–10 cm should be achieved. Transthoracic or transdiaphragmatic hiatal approaches are available, with the latter particularly suitable for localized distal oesophageal lesions and resulting in less operative morbidity than thoracotomy.
— biopsy/partial oesophagectomy/total thoracic oesophagectomy (TTO)/oesophagectomy with limited gastrectomy/oesophagogastrectomy.
— procedure: transthoracic or transhiatal.
— number of fragments/length of oesophagus and proximal stomach (cm). Measurements are better assessed on the fresh specimen as formalin fixation causes up to 30% contraction. The external surface is also inspected for the presence of adventitial fat, lateral mediastinal pleura and distally abdominal peritoneum.

Tumour

Site

— mid/lower oesophagus/oesophagogastric junction/cardia. Tumour is considered oesophageal if >50% of its mucosal bulk or epicentre is

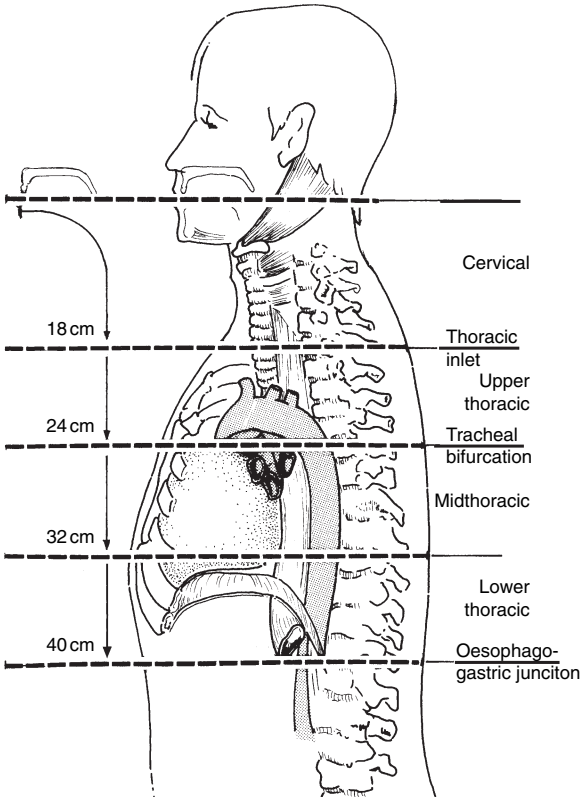


FIGURE 1-1. Oesophagus.

above the oesophagogastric junction as defined by internal or external landmarks, i.e. where the tubular oesophagus ends and the saccular stomach begins. Equally, adjacent oesophageal Barrett's metaplasia or mucosal dysplasia indicates an oesophageal lesion, and gastric mucosal dysplasia a gastric tumour.

— distances (cm) to the proximal and distal resection limits and the oesophagogastric junction. The junction can vary in location or be obscured by tumour and anatomically distal oesophagus has an external layer of adventitia or abdominal peritoneum whereas proximal stomach is oriented to serosa. Distinction is important as the TNM staging and mode of spread differ. Tumours involving the junction are classified as either Siewert I (distal oesophagus growing down), II (truly junctional) or III (gastric cardia growing up). Siewert

I is staged as oesophageal under TNM rules, Siewert II and III as gastric. In addition, squamous cell, small cell and undifferentiated carcinomas involving the junction are regarded as oesophageal in origin.

Size
— length × width × depth (cm) or maximum dimension (cm).
— superficial carcinoma is often small (<2–3 cm long) but advanced carcinoma frequently involves long segments of oesophagus.

Appearance
— polypoid: spindle cell carcinoma with good prognosis.
— warty/verrucous: verrucous carcinoma.
— nodular/plaque: superficial carcinoma (the gross and endoscopic appearances may be classified similar to that of early gastric cancer; see Chapter 2).
— fungating/stricture/ulcerated/infiltrative: usual types.
— multifocal (10%).
— regression and scarring post neoadjuvant chemo-/radiotherapy.

Edge
— circumscribed/irregular.

Other pathology
— fistula/perforation either spontaneous, post adjuvant therapy or post endoscopy.
— diverticulum.
— achalasia.
— Barrett's metaplasia: velvety mucosa distinct from the pale squamous mucosa and proximal to the junction.
— male preponderance (3:1).

2. HISTOLOGICAL TYPE

Adenocarcinoma
— 50–60% of cases.
— distal oesophagus/oesophagogastric junction on the basis of specialized enteric-type Barrett's metaplasia and dysplasia. The incidence of this tumour has greatly increased (×3–5 in the last 20 years). Various suggested factors are heredity, improved socio-economic conditions with obesity from a Western diet rich in processed foods, antibiotic eradication of acid-suppressing pangastric cag-A (cytotoxin-associated gene product)-positive Helicobacter pylori with restoration of gastric acidity and increased gastro-oesophageal reflux disease, proton pump inhibitor therapy and bile reflux. Most are tubular or papillary and of intestinal type, some are signet ring cell or mucinous. Prognosis is poor as presentation is at a late stage, typically with perineural invasion.

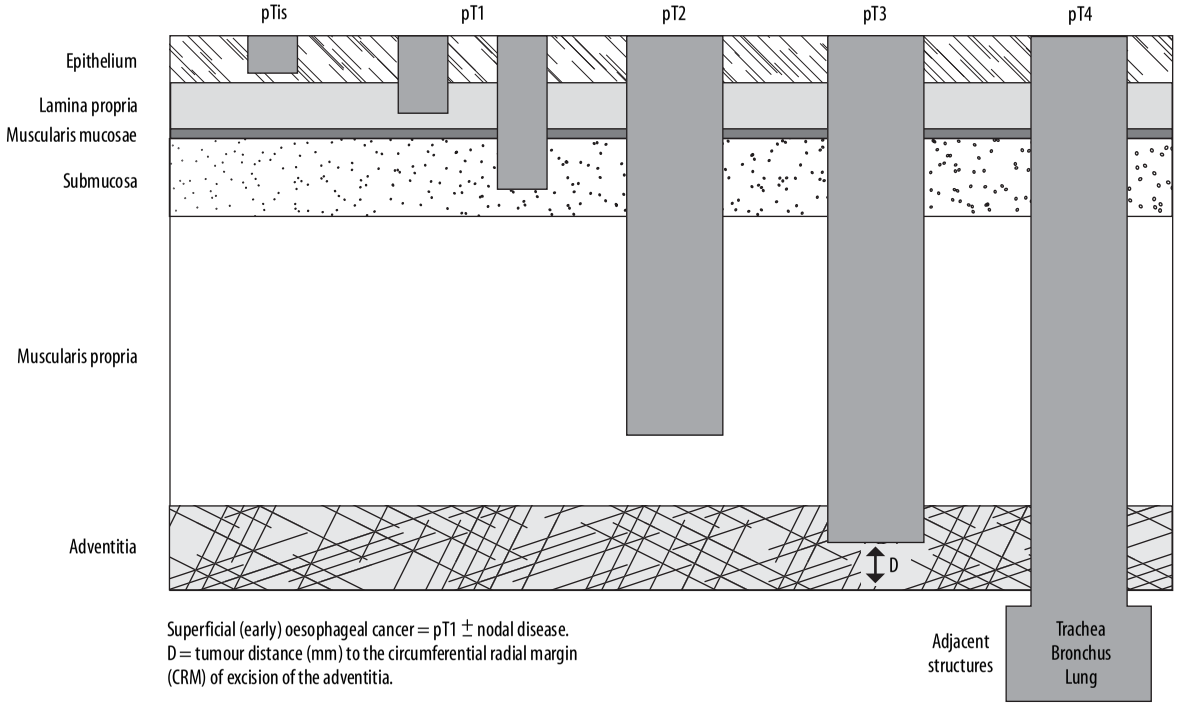


FIGURE 1.2. Oesophageal carcinoma.

Squamous cell carcinoma
— 30–40% of cases.
— mid-oesophagus, old age.
— usually moderately differentiated keratinizing.
— verrucous: exophytic and keratotic with a pushing deep margin of cytologically bland bulbous processes. Slow growing but anecdotally may become more aggressive, especially after radiation.
— basaloid: poor prognosis and aggressive. Deeply invasive nested pattern of palisaded basaloid cells with central necrosis, atypia and mitoses. Often admixed with usual squamous carcinoma.

Spindle cell/sarcomatoid carcinoma (polypoid carcinoma/carcinosarcoma)
— a spindle cell squamous carcinoma that undergoes varying degrees of stromal mesenchymal differentiation.
— men, sixth decade.

Adenosquamous carcinoma
— mixed differentiation, aggressive.

Undifferentiated carcinoma
— no distinct squamous or glandular differentiation features and a high-grade lesion.
— in poorly differentiated lesions adenocarcinoma may be CK7/CAM5.2 positive and squamous cancer negative for these markers. Characterization is of use as squamous cancers are often more responsive to adjuvant therapy and can be associated with synchronous or metachronous upper aerodigestive tract tumours.

Mucoepidermoid/adenoid cystic carcinoma
— of oesophageal submucosal duct origin. Tendency to local recurrence and metastases in 50%.

Small cell carcinoma
— primary or secondary from lung, or as part of a mixed differentiation oesophageal cancer. Poor prognosis. Distinguish from poorly differentiated basaloid squamous cell or adenocarcinoma by chromogranin/synaptophysin/CD56 and paranuclear dot CAM5.2 expression.

Malignant melanoma
— primary or secondary. Primary requires adjacent mucosal junctional atypia. Comprises 0.1% of oesophageal malignancy—polypoid, ulcerated, satellite nodules, pigment, poor prognosis.

Metastatic carcinoma
— direct spread: stomach, thyroid, hypopharynx, bronchus and lung
— distant spread: breast, malignant melanoma.

3. DIFFERENTIATION

Well/moderate/poor/undifferentiated, or Grade 1/2/3/4.

— influence on prognosis is uncertain unless the tumour is anaplastic, e.g. undifferentiated carcinoma, small cell carcinoma or basaloid carcinoma.
— for squamous cancers differentiation features are keratinization and intercellular bridges, and for adenocarcinomas the percentage tumour gland formation (well/G1 >95%: moderate/G2 50–95%: poor/G3 <50%). Undifferentiated carcinomas cannot be categorized as either squamous cell or adenocarcinoma and are classified as Grade 4 (as is small cell carcinoma).
— heterogeneity of differentiation within individual tumours is not uncommon.

4. EXTENT OF LOCAL TUMOUR SPREAD

Border: pushing/infiltrative.
Lymphocytic reaction: prominent/sparse.
Depth (cm) and distance (mm) to the nearest painted perioesophageal circumferential resection margin.

Superficial or "early" squamous carcinoma of the oesophagus is defined as intraepithelial or invasive squamous carcinoma confined to the mucosa or submucosa, with or without lymph node spread (pTis, pT1) and is of more favourable prognosis than the usual muscle invasive deep or "advanced" carcinoma (60–90% 5-year survival rates versus 5–10%). Carcinoma invading submucosa does less well (35% nodal metastases, 55% 5-year survival) than that confined to the mucosa alone (88% 5-year survival irrespective of nodal status). Depth of invasion is the most important prognostic indicator on multivariate analysis and requires histological assessment as there is variable correlation with gross, radiological and endoscopic appearances. Note that on biopsy distinction between dysplastic glands or squamous epithelium abutting an irregular muscularis mucosae and true invasion can be difficult: look for single cells and nests of infiltration (± a desmoplastic stromal reaction). The edge of a well-differentiated adenocarcinoma may manifest as mildly atypical glands devoid of stromal reaction but undermining oesophageal squamous epithelium. However, the pitfall of treatment-related squamous re-epithelialization overlying Barrett's mucosa (± dysplasia) must also be borne in mind.

The TNM classification applies only to carcinomas.

pTis	carcinoma in situ
pT1	tumour invades lamina propria or submucosa*
pT2	tumour invades muscularis propria
pT3	tumour invades adventitia
pT4	tumour invades adjacent structures.†

*Potential descriptors: pT1a (lamina propria), pT1b (submucosa).
†Trachea, bronchi, pleura, lung, pericardium, heart, aorta, vena cava, azygos vein.

About 50% of distal oesophageal carcinomas spread into the proximal stomach with potential for serosal involvement. Junctional and gastric tumour components are regarded as gastric in site for TNM staging.

In cases with post neoadjuvant therapy regression, ypT is determined by the deepest residual viable tumour and not more deeply placed keratin debris where tumour may have been.

5. LYMPHOVASCULAR INVASION

Present/absent.

Intra-/extratumoral.

The presence of lymphovascular invasion (LVI) is a strong prognostic indicator. In advanced carcinoma lamina propria and submucosal LVI are not infrequent, resulting in carcinomatous emboli several centimetres beyond the gross tumour edge. These skip metastases are not classified separately under TNM. Perineural invasion is also characteristic.

6. LYMPH NODES

The significance of nodal micrometastases (≤2 mm diameter) is uncertain but involvement of lymph nodes, particularly if multiple, is a strong prognostic indicator. Nodal metastases occur early in the disease course and are the commonest cause of treatment failure. Histological assessment is required as specificity of lymph node involvement on endoluminal ultrasound is limited. Involvement of stomach and later liver, lungs and adrenal gland is not infrequent.

Site/number/size/number involved/limit node/extracapsular spread.

Regional nodes: cervical oesophagus—cervical/supraclavicular; intrathoracic oesophagus—perioesophageal/subcarinal/mediastinal/perigastric excluding coeliac. A mediastinal lymphadenectomy will ordinarily include a minimum of six regional lymph nodes.

pN0	no regional lymph node metastasis	
pN1	metastasis in regional lymph node(s)*	
pM1	distant metastasis	
	commonest sites are mediastinum, lung and liver	
	tumour thoracic oesophagus	
	lower	M1a coeliac nodes
		M1b other distant metastasis
	upper	M1a cervical nodes
		M1b other distant metastasis
	mid	M1b distant metastasis
		including non-regional nodes.

7. EXCISION MARGINS

Distances (cm) to the proximal and distal limits of excision.

Distance (mm) to the painted perioesophageal circumferential radial margin. Involvement (tumour present to within 1 mm) is an index of the

*Potential descriptors: pN1a (1–3), pN1b (4–7), pN1c (>7 nodes involved).

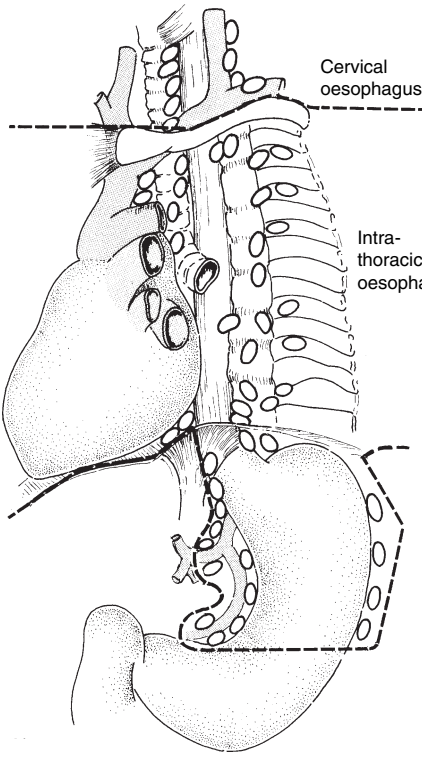


FIGURE 1.3. Oesophagus: regional lymph nodes.

degree of tumour spread and extent of surgical resection with potential for local recurrence or residual mediastinal disease.

Oesophageal carcinoma may show multifocality (10–25%), direct or discontinuous submucosal and lymphovascular spread and intramural metastasis (15%). This has obvious implications for examination of resection margins and potential for local recurrence.

8. OTHER PATHOLOGY

Diverticula, achalasia, coeliac disease and Plummer–Vincent syndrome have an increased incidence of oesophageal carcinoma.

Barrett's metaplasia: defined as replacement of the lower oesophageal squamous mucosa by metaplastic glandular epithelium due to gastro-oesophageal reflux disease. The Barrett's segment can be classical (>3 cm long) or short (<3 cm long) with, in particular, long segment disease having an increased risk of malignancy. Ultra-short segment Barrett's is now regarded as junctional metaplasia, a separate condition related to

Helicobacter pylori infection or reflux. An approximate guide is that 10% of patients with hiatus hernia and/or gastro-oesophageal reflux develop Barrett's metaplasia and that 10% of these subsequently have dysplasia or adenocarcinoma with a × 30–40 risk that of the general population, although this may be an overestimate. The specialized intestinal or enteric variant of Barrett's metaplasia is the usual precursor to dysplasia rather than the atrophic gastric fundic or non-specialized cardia types. The biological behaviour of low-grade dysplasia is uncertain with potential for regression after PPI (proton pump inhibitor) treatment or progression. It requires reassessment and if a higher grade lesion is excluded, subsequent 6-monthly endoscopic surveillance. There is a strong (30–40%) association between high-grade dysplasia and concurrent or subsequent adenocarcinoma, indicating the need for immediate clinicopathological reassessment, short-term follow-up and consideration of surgery. The recognition of significant dysplasia requires confirmation by a second experienced pathologist or positive repeat biopsy. Useful clues to the presence of dysplasia are mucosal villousity and persistence of cytological dysmaturation into the surface epithelium. Observer agreement rates are reasonably high for high-grade dysplasia. However, it is important to distinguish florid regenerative changes in oesophageal squamous and glandular mucosae from dysplasia taking into account erosion, ulceration and the degree of inflammation that is present as well as cytoarchitectural changes, e.g. nuclear enlargement with nucleolar prominence and basal cell hyperplasia. Squamous epithelial regrowth with anti-reflux, laser or photodynamic ablative therapy can produce variably atypical and confusing cytoarchitectural changes, as does chemo-/radiation therapy. Maturation towards the epithelial surface is reassuring. Over-expression of p53 antibody and a high Ki67 proliferation index (especially in the surface epithelium) may help to confirm mucosal dysplasia and its potential for progression to carcinoma in dysplastic Barrett's mucosa, although they are not routinely applicable. It should be noted that the primary diagnosis of Barrett's metaplasia (columnar lined oesophagus) is heavily dependent on the endoscopic findings and site of biopsy, i.e. an origin from the anatomical oesophagus. Pathognomonic histological features are metaplastic glandular epithelium associated with native oesophageal structures, e.g. submucosal glands or ducts. Glandular mucosa with squamous epithelial islands is also a useful clue. Specialized enteric differentiation is reasonably distinctive, whereas fundic or cardia gastric mucosa is more often associated with hiatus hernia. Surveillance for dysplasia in Barrett's mucosa is recommended as annual or biennial endoscopy with quadrantic, segmental (every 2 cm) biopsies. Target biopsy of any gross lesion (ulcers, nodules, plaques, strictures) is important, as this is more likely to yield significant pathology.

Field change dysplasia/carcinoma in situ: may be encountered adjacent to or overlying squamous cell carcinoma. A precancerous phase and the biological course of these premalignant changes is uncertain but better established in countries such as China and Japan, where the incidence

of oesophageal carcinoma is greater. This has led to the establishment of endoscopic and cytological screening programmes targeted at the early detection of lesions. As with glandular dysplasia, a two-tiered system of low- and high-grade dysplasia is used. Dysplasia is found more frequently overlying and adjacent to superficial than advanced squamous cell carcinoma.

Concurrent squamous cell carcinoma of bronchus and oropharyngolaryngeal ring has an incidence of 10–15%. Bronchoscopy and upper airways endoscopy should be carried out prior to radical treatment to exclude a lung cancer spreading to involve the oesophagus.

Radio-/chemotherapy necrosis and tumour regression: cell apoptosis, vacuolation and degeneration, necrosis, inflammation, fibrosis, residual aggregates of keratin with a giant cell reaction and perforation may all be seen leaving only residual microscopic tumour. Radiotherapy is the main treatment for extensive squamous carcinoma of the middle third of the oesophagus, and surgery for medically fit patients with locally confined lesions <5 cm in length and cancers of the distal third. Preoperative chemo-/radiotherapy is being increasingly used in an attempt to downstage the tumour and achieve better operative resectability. It is estimated that some 50–60% of tumours show quite marked morphological changes of regression, with squamous carcinoma being more radioresponsive than equally chemoresponsive adenocarcinoma. More sophisticated preoperative staging (e.g. CT/PET scan and endoluminal ultrasound with fine-needle aspiration cytology) is being assessed as a means of predicting those patients likely to benefit from preoperative adjuvant therapy and in selecting patients with locoregional confined disease for resection. Ablative laser therapy and insertion of an expansile metal stent are additional palliative measures for bulky tumour.

Carcinosarcoma: cytokeratin and mesenchymal markers (vimentin, desmin, actin) are helpful in spindle cell/sarcomatoid carcinoma. These tumours show a biphasic spectrum of malignant epithelial (squamous) and mesenchymal (usually sarcoma not otherwise specified, sometimes cartilage, bone, striated muscle) differentiation with either intimate intermingling or juxtaposition of the components that are present in variable amounts (the epithelial component may be microscopic or in situ). Prognosis is intermediate to good because they are exophytic intraluminal lesions which present at a relatively early stage despite their size (50% 5-year survival).

Squamous cell carcinoma is common in the mid-thoracic oesophagus, while Barrett's-related adenocarcinoma is commoner, being the most frequent malignant tumour of the distal oesophagus. The incidence of Barrett's-related adenocarcinoma is markedly increasing, along with that of oesophagogastric junctional lesions.

Prognosis

Prognosis of oesophageal cancer is poor (5-year survival 5–10% in the Western hemisphere) and relates to tumour type (small cell carcinoma,

basaloid carcinoma are adverse), grade (equivocal), diameter (in superficial carcinoma), but most importantly, depth of invasion and stage. Nodal status and whether the longitudinal and circumferential radial margins are positive (55% recurrence rate, 25% 5-year survival) or negative (13% recurrence rate, 47% 5-year survival in one series) are important prognostic variables. Early oesophageal squamous cell carcinoma does significantly better than advanced disease. Early (pT1) adenocarcinoma may show less recurrence than equivalent squamous lesions but, for the majority of cases, although adenocarcinoma may have slightly better overall 5-year survival (25%), the two main pathological types have little differential influence on prognosis.

9. OTHER MALIGNANCY

Lymphoma/leukaemia

— rare. More usually secondary to systemic/nodal disease.
— primary lymphoma is large B cell in type.
— consequences of immunosuppression due to the tumour or its treatment may be seen, e.g. cytomegalovirus, herpetic or fungal oesophagitis.

Leiomyoma/ leiomyosarcoma/GISTs

— leiomyomas greatly outnumber leiomyosarcomas (malignancy: >5 cm diameter, necrosis, mitoses >5/50 high-power fields, cellular atypia, infiltrative margins). Most are small, identified by endoscopy and arise from the muscularis mucosae or inner muscularis propria. They can be multiple, intraluminal or intramural. Oesophageal gastrointestinal stromal tumours (GISTs) are rare (CD117/CD34 positive, desmin negative) and potentially malignant with liver metastases.

Sarcoma

— rare. Ninety percent are leiomyosarcoma (desmin, h-caldesmon positive).
— embryonal rhabdomyosarcoma (childhood: desmin/myo D1/myogenin positive).
— Kaposi's sarcoma (AIDS): human herpes virus 8 (HHV 8) positive by polymerase chain reaction.
— synovial sarcoma: children/adults, polypoid mass in upper oesophagus.
— exclude the more common possibility of a spindle cell carcinoma (polypoid carcinoma/carcinosarcoma) with cytokeratin-positive spindle cells and varying degrees of homologous or heterologous mesenchymal differentiation.

Others

— rare: granular cell tumour (S100 positive, overlying pseudoepitheliomatous hyperplasia), carcinoid tumour (chromogranin, synaptophysin, CD56 positive).

2
Gastric Carcinoma

1. GROSS DESCRIPTION

Specimen

— gastric cancer can present with anaemia, weight loss or dyspeptic symptoms. Investigation is by endoscopy with biopsy. Staging for local and distant disease includes ELUS (endoluminal ultrasound: tumour depth and nodal spread), CT scan chest, abdomen and pelvis, PET scan and peritoneal laparoscopy with cytological washings and biopsy. Non-regional disease is an indicator for palliative treatment including chemotherapy, and surgery if there is anatomical dysfunction, e.g. extensive ulceration and bleeding or gastric outlet obstruction. Curative intent surgery can be localized [e.g. endoscopic mucosal resection (EMR)] or radical, the extent of the latter depending on the patient's age, fitness, tumour type, stage and location.
— cytological brushing, washing or aspirate/biopsy/ partial (proximal or distal) or total gastrectomy/oesophagogastrectomy/lymphadenectomy ± omentectomy.
— length (cm) along greater curvature.
— length (cm) of oesophagus and duodenum.

Tumour

Site

— distal oesophagus/cardia/fundus/corpus/antrum/pylorus/duodenum.
— lesser curve/greater curve.
— anterior/posterior.

Antrum (50%) and lesser curve (15%) are traditionally the most frequent sites. However, the incidence of distal gastric carcinoma is decreasing while that of the proximal stomach and cardia is markedly increasing. This is in part due to eradication of Helicobacter pylori infection and loss of its acid suppression effect and more reflux changes. It presents at a more advanced stage than equivalent-size distal lesions with a worse prognosis and similarities in behaviour to distal oesophageal adenocarcinoma. Adenocarcinomas involving the oesophagogastric junction are TNM staged as either oesophageal (Siewert I: distal oesophagus coming

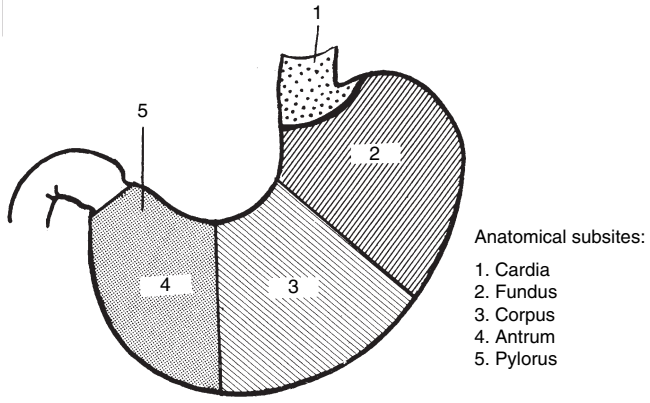


FIGURE 2.1. Stomach.

down) or gastric (Siewert II: junctional, Siewert III: gastric cardia going up).

— multifocal 6%: in particular early gastric cancer and lymphoma.

Size

— length × width × depth (cm) or maximum dimension (cm).

Appearance

— polypoid/plaque/ulcerated/infiltrative/mucoid/linitis plastica/scirrhous/fleshy.

Advanced (muscle invasive) gastric cancer is classified macroscopically according to Borrmann type as:

I polypoid
II fungating
III ulcerated
IV infiltrative.

Types I, II/III and IV tend to correspond to tubulo/papillary, intestinal and signet ring cell (linitis plastica) adenocarcinoma, respectively, although there is overlap between the categories. Polypoid/ulcerated tumours are regarded as being of better prognosis than infiltrative cancers.

Edge

— circumscribed/irregular.

2. HISTOLOGICAL TYPE

An amalgam of the WHO and Lauren* classifications is used

Adenocarcinoma

*intestinal	50%	antrum
*diffuse	20%	body of stomach, young or old patients
*mixed	25%	
*solid	5%	

Intestinal carcinomas have tubuloacinar (common), papillary or mucinous (colloid) patterns, form polypoid or ulcerative lesions with expansile margins and are associated with atrophic gastritis, intestinal metaplasia and dysplasia. By definition tubular adenocarcinoma is well differentiated and may be difficult to diagnose due to wide separation of glands in a non-desmoplastic stroma. Undermining of structures can be helpful, e.g. muscularis mucosae or oesophagogastric junction squamous epithelium. Equally, papillary adenocarcinoma is exophytic with well-differentiated epithelial fronds supported by fine fibrovascular stroma. Biopsies may only sample its surface component and distinction from high-grade dysplasia can be problematic. Its endoscopic and ELUS/CT appearances and sharp demarcation from adjacent mucosa must be taken into account. The definition of a mucinous adenocarcinoma, whether glandular, colloid or signet ring cell, requires mucin production in >50% of the tumour area or cells.

Diffuse carcinomas comprise single cells with signet ring or granular cytoplasmic appearances and form linitis plastica with infiltrating margins. A point of origin from dysplasia is often difficult to demonstrate and the tumour emanates from the mid-mucosal proliferative zone (from non-metaplastic foveolar or mucous neck cells), or deep lamina propria invading submucosa, muscularis, serosa and into the peritoneal cavity. The cells do not express the adhesion protein E-cadherin. A minority (8–10%) of gastric cancers are hereditary and in a young patient occult presentation with an inherited autosomal dominant diffuse gastric cancer should be considered. Alternatively, intestinal gastric cancer can develop in a young patient as part of the hereditary non-polyposis colon cancer syndrome (HNPCC).

Adenocarcinoma variants

Hepatoid carcinoma: glandular and hepatocellular differentiation with marked vascular invasion and poor prognosis. ±AFP (alphafetoprotein) immunoexpression, polyclonal carcinoembryonic antigen (CEA) positive.

Parietal cell carcinoma: rare. Solid sheets of cells with eosinophilic granular cytoplasm.

Medullary carcinoma (syn. lymphoepithelial carcinoma): circumscribed with a dense lymphoplasmacytic infiltrate, regular vesicular nuclei and small nucleoli.

77% 5-year survival and associated with Epstein–Barr virus infection and HNPCC.

Adenosquamous carcinoma and squamous cell carcinoma

— rare: need keratinization and intercellular bridges. Vascular invasion and aggressive.

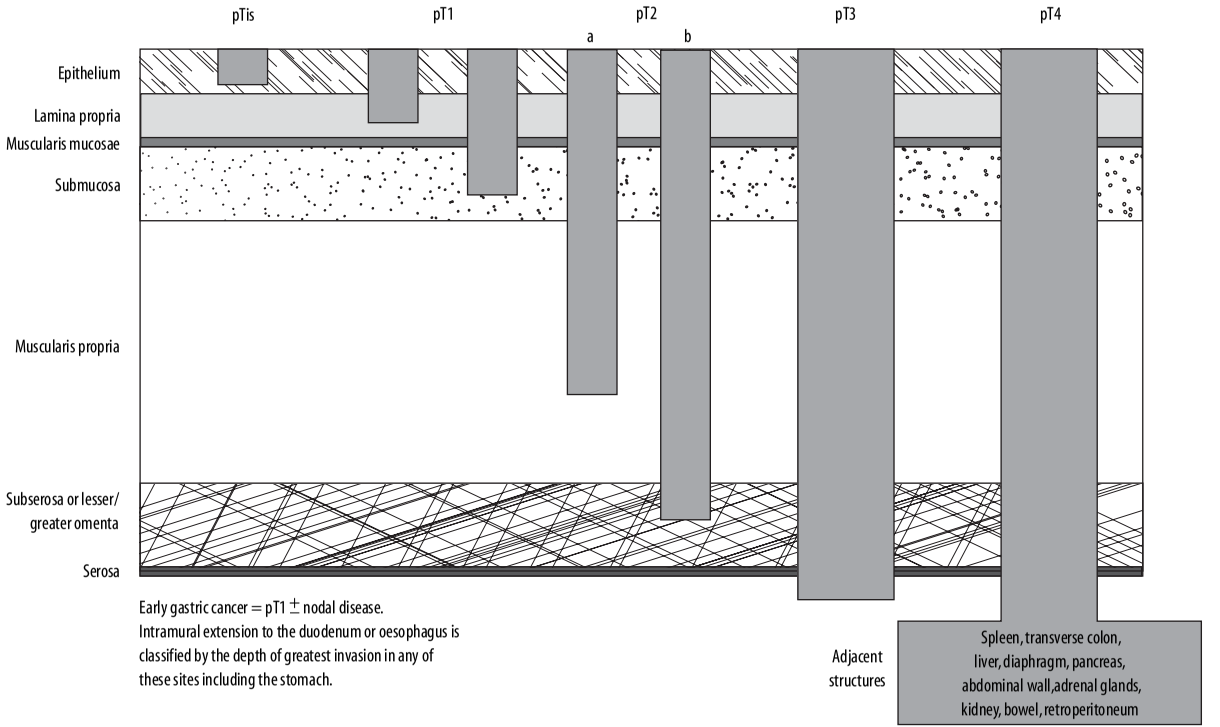


FIGURE 2.2. Gastric carcinoma.

Undifferentiated carcinoma
— cytokeratin positive but no histological differentiation features.

Neuroendocrine carcinoma
— carcinoid, small cell/large cell carcinoma.

Lymphoma
— low/high-grade MALToma.
— less commonly: diffuse large B-cell lymphoma, follicle centre cell lymphoma, mantle cell lymphoma, T-cell lymphoma.

Metastatic carcinoma
— direct spread: pancreas, oesophagus, transverse colon.
— distant spread: small cell carcinoma lung, malignant melanoma, breast, kidney, choriocarcinoma, ovary.
— metastatic infiltrating lobular carcinoma of breast can mimic signet ring cell carcinoma of stomach and a known clinical history of a previous breast primary is crucial to the diagnosis. Breast cancer may also be ER/PR/GCDFP-15/cytokeratin 7 positive and cytokeratin 20 negative. Note that a significant minority of gastric adenocarcinomas may also be oestrogen receptor positive.

3. DIFFERENTIATION

Well/moderate/poor/undifferentiated, or Grade 1/2/3/4.

For adenocarcinoma based on the percentage tumour gland formation (well/G1 >95%: moderate/G2 50–95%: poor/G3 <50%).

Undifferentiated gastric carcinoma (grade 4) shows no glandular differentiation and requires positive cytokeratin stains to distinguish it from lymphoma or sarcoma. Signet ring cell carcinoma is regarded as poorly differentiated (grade 3) and small cell carcinoma as undifferentiated (grade 4).

Goseki grade—based on mucin secretion and tubule formation:

I tubules well differentiated, mucin-poor
II tubules well differentiated, mucin-rich
III tubules poorly differentiated, mucin-poor
IV tubules poorly differentiated, mucin-rich.

Well-differentiated (tubule-rich) mucin-poor cancers have better (50–80%) 5-year survival rates than moderately or poorly differentiated (tubule-poor) mucin-rich tumours (18–46%).

4. EXTENT OF LOCAL TUMOUR SPREAD

Border: pushing/infiltrative.

Well-circumscribed tumours have longer patient survival than infiltrating cancers (except in early gastric cancer).

Lymphocytic reaction: prominent/sparse.

Gastric cancer is considered as either early (pT1) or advanced (≥pT2) as there is prognostic discrepancy between these two levels of invasion.

The TNM classification applies only to carcinomas.

pTis carcinoma in situ: intraepithelial tumour without invasion of the lamina propria
pT1 tumour invades lamina propria or submucosa*
pT2 tumour invades muscularis propria or subserosa or lesser/greater omenta
  a. muscularis propria
  b. subserosa or omentum
pT3 tumour penetrates serosa (visceral peritoneum) without invasion of adjacent structures
pT4 tumour invades adjacent structures (spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, retroperitoneum).

The lesser omentum includes the gastrocolic and gastrohepatic ligaments and involvement of their peritoneal covering constitutes pT3 disease. There is decreased post surgical 5-year survival for pT2b versus pT2a cancer. Discontinuous greater omental tumour nodules are classified as metastatic disease (pM1).

Intramural extension to the oesophagus or duodenum is classified by the depth of greatest invasion in any of these sites.

Diffuse gastric carcinoma may not elicit a desmoplastic stroma and the depth of mural invasion, which is often extensive and can be characterized by small, inapparent non-mucinous tumour cells in the muscularis propria and adventitia, may be underestimated. Equally, margin status can be incorrectly assessed. Stains [periodic acid–Schiff (PAS) ± diastase, cytokeratins, CEA, epithelial membrane antigen (EMA)] should be used to show its full extent and also to distinguish tumour cells from histiocytes in both the mucosa and lymph node sinus network.

5. LYMPHOVASCULAR INVASION

Present/absent.
Intra-/extratumoral.
Venous, lymphatic and perineural invasion are adverse prognostic factors.

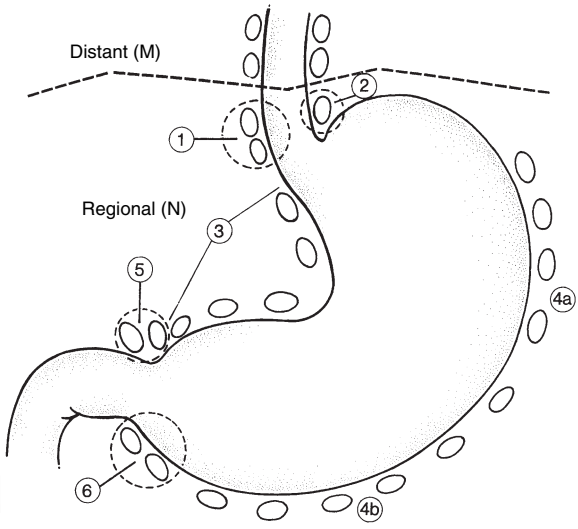
Intestinal gastric adenocarcinoma tends to venous invasion with spread to liver, lung, adrenal glands and bone, whereas diffuse gastric carcinoma favours lymphatic and direct peritoneal spread. Bilateral ovarian metastases from diffuse gastric cancer comprise the majority of Krükenberg tumours. Uterine body and cervix can also be involved by metastatic disease.

6. LYMPH NODES

Site/number/size/number involved/limit node/extracapsular spread.

Regional nodes: perigastric, hepatoduodenal, nodes along the left gastric, common hepatic, splenic and coeliac arteries. Other intra-

*Potential descriptors: pT1a (lamina propria), pT1b (submucosa).



The regional lymph nodes are the perigastric along the lesser (1,3,5) and greater (2,4a,4b,6) curvatures, the nodes located along the left gastric (7), common hepatic (8), splenic (10,11) and coeliac arteries (9) and the hepatoduodenal nodes (12). The regional nodes of the gastrooesophageal junction are the paracardial (1,2), left gastric (7), coeliac (9), diagphragmatic and the lower mediastinal paraoesophageal. Involvement of other intra-abdominal lymph nodes such as retropancreatic, mesenteric and para-aortic is classified as distant metastasis.

FIGURE 2.3. Stomach: regional lymph nodes. W

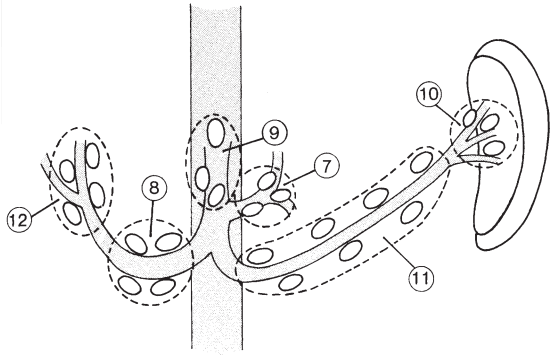


FIGURE 2.4. Stomach: regional lymph nodes. W

abdominal lymph nodes are distant metastases (pM1). A regional lymphadenectomy will ordinarily include a minimum of 15 lymph nodes but numbers depend on the extent of surgery. In a D1 resection only perigastric lymph nodes are excised. In a D2 (radical) gastrectomy there is additional nodal dissection along the hepatic artery, coeliac plexus, greater omentum, gastroplenic omentum, portal vein, splenic artery and retropancreatic area. The surgeon may choose to submit these in separately labelled containers.

pN0 no regional lymph node metastasis
pN1 1 to 6 involved regional nodes
pN2 7 to 15 involved regional nodes
pN3 more than 15 involved regional nodes.

Five-year survival decreases with increasing numbers of involved lymph nodes.

7. EXCISION MARGINS

Distances (mm) to the radial, proximal and distal limits of excision.

Gastric carcinoma (especially diffuse signet ring cell) may show multifocality and submucosal skip lesions. Margins need to be checked histologically even if well away from the main tumour mass on gross examination. Diffuse carcinoma present to within 5 cm of the resection margin has an adverse prognosis. Distal intestinal cancers tend to stop at the pylorus while diffuse carcinoma may involve the first part of the duodenum. Proximal (cardia) tumours often involve distal oesophagus (Siewert III).

The radial margin is the non-peritonealized lesser or greater omental margin closest to the tumour. It can be inspected and inked prior to blocking.

8. OTHER PATHOLOGY

Early gastric cancer (EGC)

Forming 10–15% of gastric cancers in Western countries and limited to the mucosa ± submucosa ± lymph node involvement. The 5-year survival is 85–95% compared with 20–35% for advanced gastric cancer. Designation as EGC is on a resection specimen as endoscopic biopsies are constrained by sampling limitations.

Macroscopic/endoscopic classification of EGC

Type I	protruded	10%
Type IIa	raised	80%
Type IIb	flat superficial	
Type IIc	depressed	
Type III	excavated	10%

Mixed types are common. Types I and IIa tend to be well differentiated (tubular, papillary), whereas types IIb, IIc and III also include ulcerated

intestinal, poorly differentiated and signet ring tumours, although there is considerable overlap between macroscopic and microscopic appearances.

Lesser curve is the commonest site but 10% are multifocal and require mapping of the resection specimen.

Tumours with lymph node metastases do worse than those without and tend to be large (>5 cm–80% positive nodes) or show submucosal invasion (20% positive nodes) rather than being confined to the mucosa (4% positive nodes).

Two prognostic paradoxes contrast with advanced gastric carcinoma:

1. diffuse-type EGC has a better prognosis than intestinal-type EGC due to vascular spread in the latter, and
2. EGC with a broad, expansile deep margin destroying muscularis mucosae (pen A) is more aggressive than EGC with an irregular infiltrating margin fenestrating the muscle (pen B). The tendency for pen A tumours to progress to advanced carcinoma is thought to relate to higher DNA aneuploidy rates. Pen A tumours form a minority (10%) of EGC but have higher rates of lymphovascular invasion, lymph node metastases (25%) and lower 10-year survival rates (65%),
3. i.e. well-differentiated cancers with a pushing margin do worse than poorly differentiated tumours with an infiltrating margin.

Treatment is usually by partial gastrectomy, but after appropriate clinicopathological staging local excision by endoscopic mucosal resection is possible. Risk factors predictive of nodal metastases and the need for further surgery are: size >3 cm, surface ulceration (>50%), poor differentiation, deep submucosal invasion, lymphovascular invasion and incomplete excision with deep margin involvement.

Predisposing lesions

Gastritis:* ± *Helicobacter pylori* (HP): (cresyl violet, Giemsa, Warthin–Starry stains; can assume a coccoid rather than spiral form in resections). HP-positive patients have a × 3–6 increased cancer risk, especially those with the cytotoxic (cag-A) genotype of HP.

Intestinal metaplasia:* type IIb/III (sulphomucin rich)—high iron diamine alcian blue or Gomori's aldehyde fuchsin alcian blue stains—the large intestinal variant of metaplasia is more strongly associated with mucosal dysplasia and intestinal pattern gastric adenocarcinoma. Mucin subtyping is not routinely done as it is not considered a sufficiently strong predictive factor, although the extent of intestinal metaplasia is broadly indicative.

*Classified and semi-quantitatively graded (none/mild/moderate/marked) using the Sydney classification. It classifies and grades chronic gastritis based on an assessment of histological (neutrophils, chronic inflammation, atrophy, intestinal metaplasia), topographical (antral/corpus predominant or pangastritis) and aetiological (HP, drugs) factors.

Table 2.1 Vienna Consensus Classification of gastrointestinal neoplasia

Category	Neoplasia/dysplasia
1	Negative
2	Indefinite
3	Non-invasive low grade — low-grade adenoma/dysplasia
4	Non-invasive high grade — 4.1 high-grade adenoma/dysplasia — 4.2 non-invasive carcinoma (carcinoma in situ) — 4.3 suspicious of invasive carcinoma
5	Invasive—either intramucosal*, submucosal or beyond

*A more recent proposed modification suggests categorizing intramucosal carcinoma as 4.4 as these subcategories show poor intra-/inter observer reproducibility and all require at least endoscopic or surgical local resection. Choice of procedure will depend on the lesion size, depth of invasion (as assessed by endoscopy, radiology and endoscopic ultrasound), histological grade and general features (age, fitness).

Atrophy:* ± pernicious anaemia with gastric parietal cell and intrinsic factor antibodies. 10–20% develop carcinoma.

Dysplasia: low/high-grade, either in flat (commonest), sessile or polypoid mucosa, and in metaplastic (intestinal) or non-metaplastic (gastric foveolar) mucosa. Gastrointestinal epithelial neoplasia is assessed according to the Vienna Consensus Classification (Table 2.1).

There is a strong (30–80%) association between high-grade dysplasia and adenocarcinoma either concurrently or within 1–2 years of diagnosis. Distinction between high-grade dysplasia/carcinoma in situ and lamina propria invasion can be difficult. In Europe and the USA there needs to be invasion of the lamina propria before the term (intramucosal) carcinoma is used, i.e. both cytological and architectural derangement. Eastern hemisphere pathologists require less stringent criteria. Diagnosis of dysplasia in a biopsy should be followed by reassessment with multiple biopsies to exclude concurrent carcinoma. Dye spraying can facilitate endoscopic identification. Imaging, e.g. endoluminal ultrasound, may help define a mass or infiltrative lesion. If this is absent, flat low-grade dysplasia may be monitored endoscopically while polypoid low-grade dysplasia and high-grade dysplasia in flat or polypoid mucosa should be considered for either local endoscopic or formal surgical resection. Care must be taken to distinguish dysplasia from regenerative change in inflammation and ulceration and reactive gastropathy, e.g. foveolar hyperplasia in bile reflux and drug ingestion (non-steroidal anti-inflammatory drugs, aspirin). Lack of surface epithelial maturation, budding/branching and cystically dilated deep glands are useful pointers to dysplasia.

Polyps

— hyperplastic: usual type, often antral and regenerative in nature. A 1–3% risk of malignancy* particularly if large (>2 cm) and multiple.

*Either within the polyp or elsewhere in the stomach.

— fundic gland cyst: very common. Association with colorectal pathology of various types (rare), familial adenomatous polyposis coli (FAPC) and proton pump inhibitor therapy (due to parietal cell hyperplasia secondary to hypergastrinaemia). Rarely dysplastic (FAPC).
— adenomatous: 8% of cases with a 30–40% risk of malignancy* related to size (>2 cm), villous architecture and grade of dysplasia.
— rare: FAPC, Peutz-Jeghers, Cowden's syndromes.

Ménétrier's disease and lymphocytic gastritis: hyperplastic gastropathy can be associated with adenocarcinoma.

Synchronous gastric lymphoma of mucosa associated lymphoid tissue (MALToma): also Helicobacter related.

Tumours covered by intact mucosa, such as diffuse gastric carcinoma (signet ring cell) or stromal tumours, can be difficult to demonstrate by routine biopsy and multiple biopsies with jumbo forceps may be required. Cytological brushings and washings or endoscopic fine-needle aspiration cytology may be helpful. In general, gastrointestinal cytology may yield positive information in the following situations:

a. FNA of submucosal/mural/extrinsic lesions including enlarged locoregional lymph nodes found on staging CT/ELUS
b. FNA of pancreatic mass lesions and brushings of common bile duct/pancreatic duct strictures
c. brush cytology of oesophageal and colonic strictures not amenable to usual biopsy.

Multiple (5 or 6) biopsies should be taken from ulcerated carcinomas including the ulcer base and mucosal edges. Distinction must be drawn between carcinoma and pseudomalignant changes in glandular epithelium, endothelial cells and stromal cells in erosions and ulcer base tissue. Biopsy from the base of a deeply penetrating benign peptic ulcer may yield hepatocytes or pancreatic acinar cells not to be misinterpreted as gastric adenocarcinoma. Gastric xanthoma (CD68 positive, cytokeratin and mucin negative) can also mimic diffuse gastric carcinoma and immuno markers are helpful in these situations.

Immunophenotype

Gastric carcinoma is variably neutral and acidic mucin positive (PAS-AB, mucicarmine), cytokeratin (CAM5.2, cytokeratin 7/±20), EMA and CEA positive, ±CDX-2. Diffuse carcinoma is E-cadherin negative and intestinal pattern carcinoma is positive.

Prognosis

Prognosis of gastric cancer is poor, the majority of cases presenting with advanced disease. It relates to histological type, grade and, crucially, stage. Intestinal gastric carcinoma has higher 5-year survival rates than diffuse gastric carcinoma, e.g. for pT3 lesions 42% versus 17%. Intestinal gastric carcinoma may be considered for partial gastrectomy because of its expanding margins, whereas total gastrectomy is advised for diffuse carcinoma. Additional important prognostic indicators are nodal status,

lymphovascular invasion, peritoneal and resection line involvement and an infiltrative versus an expansive tumour margin. These factors tend to outweigh other parameters such as the Lauren and Ming classification or Goseki grade. Prior to proceeding to radical surgery complete clinical staging is necessary to exclude any non-regional disease. This involves CT ± PET scan and peritoneal laparoscopy with cytology and biopsy. Pre-operative adjuvant and palliative chemotherapy have roles to play. EGC does considerably better (see above) and may be amenable to EMR.

9. OTHER MALIGNANCY

Carcinoid tumour
Chromogranin, synaptophysin, CD56 positive.

1. *Multiple* (benign): commonly associated with autoimmune atrophic gastritis and endocrine cell hyperplasia (rarely Zollinger Ellison syndrome and MEN 1). Gastric atrophy → hypochlorhydria → hypergastrinaemia → ECL (enterochromaffin-like cell) hyperplasia → microcarcinoidosis (multiple, mucosal, 1–3 mm). Can be monitored by endoscopy with biopsy excision of small polyps up to 1 cm diameter. Polyps 1–2 cm in size are treated by polypectomy or local resection as they are of malignant potential.
2. *Single* (aggressive): 13% of cases overall. If the lesion is large (>2 cm) or ulcerated consider definitive resection.
   Malignancy relates to:
   — any functioning tumour
   — angio-invasion
   — non-functioning tumour ≥2 cm diameter and with invasion beyond the submucosa
   — atypical features (atypia, necrosis, mitoses)
   — 5-year survival 70–80%
   — indolent growth with spread to nodes, liver, bone and skin.

Carcinoid cells express functional somatostatin receptors and tumours can be detected by octreotide (somatostatin antagonist) scan and treated with similar agents.

Gastrointestinal mesenchymal and stromal tumours (GISTs)
Site: stomach (60–70%), small intestine (20–30%), colorectum and oesophagus (10%). Submucosal, mural or serosal.

Myogenic: 10%—desmin/h-caldesmon/smooth muscle actin positive and c-kit negative representing true leiomyoma or leiomyosarcoma (rare).

Neural: 10%—S100/synaptophysin positive and c-kit negative Schwannoma, neurofibroma (can be associated with von Recklinghausen's disease, MEN syndrome and GISTs elsewhere in the gut).

Stromal: CD34 and CD117 (c-*kit*: tyrosine kinase receptor) positive and absent or incomplete myogenic/neural differentiation. Putative

precursors are the interstitial cells of Cajal, which are gut pacemaker cells located in the deep submucosa and myenteric plexus. Note that there can be heterogeneity and focal expression of antigens. In general, antigen positivity is CD117 (95%), CD34 (70–85%), smooth muscle actin (20–40%: high in small intestine), h-caldesmon (60–80%) and nestin (90–100%). C-kit-negative GISTs may be identified by positive protein kinase c theta and PDGFR (platelet derived growth factor receptor). Note that other malignant tumours can also be c-kit positive, e.g. seminoma, melanoma and some metastatic carcinomas, e.g. breast, ovary, colorectal, small cell carcinoma. GANT (gastrointestinal autonomic nerve tumour) is now regarded as a variant of GIST and assessed accordingly. Malignancy, which is less frequent than in small intestinal stromal tumours, cannot be accurately predicted from the histology. However, some indicators (strongest asterisked) are:

— size (>5 cm)*
— cellularity (cell density increases in sarcoma)
— atypia
— cell type (epithelioid (20%) is worse than spindle cell (70%))
— necrosis (coagulative in type)*
— margins (circumscribed versus infiltrative, e.g. invasion into mucosal lamina propria)*
— mitoses >5/50 high-power fields*
— location in fundus or gastro-oesophageal junction.
— loss of CD34 or CD117 expression and over-expression of p53.

Lesions are National Institutes of Health (NIH) categorized as very low, low, intermediate or high metastatic risk on the basis of size and mitoses (Table 2.2).

Histological grading of established sarcoma is contentious and tumour size is a suggested index of metastatic risk. Metastases are commonly to peritoneum, liver, pancreas, retroperitoneum and lungs. Metastatic disease responds well to STI 571 (Glivec, Imatinib) agent giving several disease-free years but usually therapeutic escape occurs with recurrent peritoneal disease. This may relate to the cytostatic rather than tumoricidal effects of the treatment or newly acquired mutations in the tumour cells.

Biopsy proof can be difficult as GISTs are extramucosal lesions (submucosal and mural) often with surface ulceration. Fine-needle aspiration

Table 2.2 Risk factors in GISTs

Very low risk	<2 cm	<5 mitoses/50 hpfs
Low risk	2–5 cm	<5/50
Intermediate risk	2–5 cm	6–10/50
	6–10 cm	<5/50
High risk	6–10 cm	>5/50
	>10 cm	Any rate
	Any size	>10/50

cytology at endoscopy may be helpful in establishing a diagnosis of a spindle cell lesion. The biopsy forceps may also be directed to the base of the ulcer where there is already mucosal loss.

See Chapter 4, Section 9.

Malignant lymphoma

— secondary to systemic/nodal disease or primary (commoner) in the stomach it is the commonest site for extranodal non-Hodgkin's lymphoma (40% of cases). Primary disease bulk is centred on the stomach and its regional nodes.

It can present as single or multiple lesions, a sessile plaque or thickened folds found incidentally at endoscopy, an ulcerated tumour or a thickened non-expansile stomach. The majority are of B-cell MALT (mucosa-associated lymphoid tissue) type, the low-grade variant being characterized by a proliferation of small- to medium-sized centrocyte-like cells, destructive lymphoepithelial lesions, monotypic immunoglobulin expression in surface plasma cells, invasion between or into reactive follicles (follicular colonization) and/or immunoglobulin gene rearrangements on PCR. There is evidence that localized (i.e. without deep submucosal or muscle invasion) low-grade lesions may regress on anti-Helicobacter medication and they usually pursue an indolent time course with potential metastases to other extranodal sites, e.g. gastrointestinal tract and Waldeyer's ring. They may also transform to or present as high-grade lesions necessitating chemotherapy and/or surgery, which are also applicable to extensive low-grade disease. Potential resistance to anti-Helicobacter treatment is tumour cell bcl-10 expression, presence of the t11:18 translocation (30% of cases), large cells or disease in the deep submucosa or beyond. ELUS may help to define the latter. The cytological composition of MALToma can be heterogeneous and clear distinction between a mucosal or nodal origin can be arbitrary, especially in high-grade disease. From a practical point of view establishing a B-cell phenotype, low- or high-grade character and full clinicopathological staging are the salient features relevant to management. Immunohistochemistry may also be helpful in establishing monoclonality (κ, λ light chain restriction), demonstrating lymphoepithelial lesions (cytokeratins) and lymphoma subtype (e.g. low-grade MALToma is CD45/CD20 positive but CD5, CD10, CD23 and bcl-2 negative, separating it from other low-grade B-cell lymphomas). Cytokeratins and common lymphoid antigen (CD45) are also necessary to distinguish high-grade lymphoma from undifferentiated carcinoma and signet ring or plasmacytoid change in lymphoma from signet ring cell gastric carcinoma. Low- and high-grade areas may coexist in gastric lymphoma and there can be adjacent synchronous or metachronous (up to several years later) adenocarcinoma associated with MALToma. Forty to sixty percent of gastric lymphomas are of high-grade large B-cell type and diagnosis is usually straightforward (cytological atypia/monomorphous infiltrate) with confirmatory immunohistochemistry for lymphoid markers and negative epithelial

markers. Distinction between low-grade lymphoma and lymphoid hyperplasia, as in Helicobacter pylori gastritis or peptic ulcer, can be problematic and diagnosis depends on the density of the lymphoid infiltrate and degree of gland distortion and loss. Immunoglobulin gene rearrangements provide supportive evidence, although monoclonality does not always correlate with potential for progression to malignancy and can be seen in a minority of chronic gastritis cases. Sometimes designation of low-grade lymphoma is attained only after several biopsy episodes and when there is a lack of response of the lymphoid infiltrate to eradication of Helicobacter pylori. Persistence of monoclonality over time may be helpful. Various scoring systems exist for making a diagnosis of low-grade MALToma and assessing its response to HP eradication. Minimal residual disease shows persistent basal lymphoid aggregates whereas response gives a diminished lymphoid infiltrate and fine fibrosis in the lamina propria.

Overall prognosis is reasonably good (40–60% 5-year survival), low-grade lymphomas following an indolent course (65–95% 5-year survival) but with about 50% of high-grade lymphomas being aggressive with spread beyond the stomach (40–55% 5-year survival). Prognosis relates to both grade and stage of disease at the time of presentation. Treatment of extensive low-grade and high-grade disease is with chemotherapy and/or surgery, the latter particularly if there are anatomical considerations, e.g. multifocality or bulky, ulcerated luminal disease or gastric outlet obstruction. Initial full clinical staging is carried out (CT scan, bone marrow biopsy).

Other forms of lymphoma are unusual in the stomach, e.g. follicular centre cell lymphoma, mantle cell lymphoma, Burkitt's lymphoma, anaplastic large cell lymphoma and T-cell lymphoma. Hodgkin's disease is rare.

Leukaemia

— stomach can be involved in up to 25% of cases.
— CD 68/chloroacetate esterase/myeloperoxidase positive cells (granulocytic sarcoma).

Miscellaneous rare malignancy

— Kaposi's sarcoma: visceral involvement can be present in 30–60% of AIDS patients.
— angiosarcoma, rhabdomyosarcoma, alveolar soft part sarcoma, teratoma, choriocarcinoma, yolk sac tumour.
— metastatic malignant melanoma in the stomach is now seen with increasingly powerful chemo-/immunosuppressive therapies leading to unusual patterns of metastatic disease.

3

Ampulla of Vater and Head of Pancreas Carcinoma

1. GROSS DESCRIPTION

Specimen

— pancreatic and ampullary cancers classically present with painless obstructive jaundice and investigation includes liver function tests, serum CA19-9, and OGD/ERCP with cytology and biopsy. Ultrasound can confirm duct obstruction and staging for local and distant disease also includes magnetic resonance cholangiopancreatography, CT scan chest, abdomen and pelvis and PET scan. Staging laparoscopy may also be done prior to consideration of radical surgery. Pancreatic endocrine tumours more often present as a consequence of a functional hormonal syndrome and localization of the primary lesion and metastases is by octreotide and CT scans. Treatment entails complete local excision of the primary tumour with a combination of surgery and medical treatment for metastatic disease.
— endoscopic brushings or biopsy/transduodenal or percutaneous fine-needle aspirate (FNA) or needle core biopsy.
— Whipple's procedure (partial gastrectomy, duodenectomy and partial pancreatectomy). A pylorus-preserving pancreaticoduodectomy may be used for small peri-ampullary tumours, thus maintaining the storage and release functions of the distal stomach and proximal 3 cm of duodenum.
— total pancreatectomy (partial gastrectomy, duodenectomy, total pancreatectomy and splenectomy).
— weight (g) and size/length (cm), number of fragments.

Carcinomas of the ampulla and head of pancreas are considered together because of their anatomical juxtaposition, overlap and common potentially operative resection (Whipple's procedure). A majority of ampullary cancers are operable but only a minority of pancreatic carcinomas.

Tumour

Site

— non-ampullary duodenal mucosa/duodenal papilla/ampullary mucous membrane/muscularis/pancreatic head (60–70% of pancreatic carcinomas)/terminal common bile duct/multifocal.

Size
— length × width × depth (cm) or maximum dimension (cm).

Ampullary cancers >2.5 cm diameter have a decreased 5-year survival. Pancreatic exocrine cancers >3 cm are often inoperable. Pancreatic endocrine tumours >2–3 cm show greater local and vascular invasion and metastatic potential.

Appearance
— polypoid/nodular/diffuse/ulcerated: ampullary tumours.
— scirrhous/mucoid/cystic: pancreatic exocrine tumours.
— circumscribed/pale: pancreatic endocrine tumours.

Edge
— circumscribed/irregular.

2. HISTOLOGICAL TYPE

Ampulla
— adenocarcinoma. 80% of cases are usually of well to moderately differentiated intestinal pattern arising from adenomatous dysplasia in the peri-/intra-ampullary mucosa. Endoscopic biopsy underestimates the nature and extent of disease yielding a positive diagnosis of malignancy in only about 40% of cases. It samples the surface dysplasia but not the underlying carcinoma, which is better demonstrated as a mass lesion on imaging (ELUS, CT).
— papillary adenocarcinoma. Exophytic, well differentiated of better prognosis and can be multifocal in the extrahepatic biliary tree.
— mucinous adenocarcinoma—mucin in >50% of the tumour.
— signet ring cell adenocarcinoma.
— metastatic carcinoma, e.g. direct spread: stomach, pancreas, terminal common bile duct. Some 10–15% of ampullary adenocarcinomas arise from the terminal portion of either of the main ducts and, therefore, have a biliary phenotype making distinction from invasion by pancreatic adenocarcinoma difficult.

Pancreas

(a) Exocrine
— ductal adenocarcinoma (80–90% of cases):
tubulo-acinar pattern of malignant ductal epithelium in a desmoplastic stroma with perineural invasion and dysplasia of the adjacent duct epithelium (20–30%). Pancreatic intraepithelial neoplasia (PanIN) is a microscopic papillary or flat, non-invasive epithelial neoplasm (dysplasia) comprising cubocolumnar epithelial cells with variable degrees of cytoarchitectural atypia. It usually arises in pancreatic ducts <5 mm diameter, is multifocal and seen adjacent to existing carcinoma, being regarded as a precursor to it. High-grade PanIN is

equivalent to severe dysplasia or carcinoma in situ. Note that PanIN can be mimicked by florid reactive atypia or cancerization of ducts by invasive ductal carcinoma.
multifocality 15–40%.
male preponderance.

— ductal adenocarcinoma variants:
mucinous non-cystic colloid carcinoma (1–3%): mucin in >50% of the tumour.
adenosquamous: at least 30% squamous component.
microglandular/signet ring cell—poor prognosis. Exclude a gastric carcinoma secondary deposit.
oncocytic.
clear cell.

— undifferentiated carcinoma (2–7%: syn pleomorphic/giant cell/sarcomatoid carcinoma):
spindle cells/pleomorphic cells/mitoses/lymphovascular invasion. Variant with osteoclast-like giant cells may have a slightly better prognosis.

— intraductal papillary or mucinous neoplasms/tumours (IPMNT):
IPMNT is a clinically detectable grossly visible, non-invasive, mucin-producing papillary epithelial neoplasm. It arises from the main pancreatic duct or branch ducts with varying duct dilation (>1 cm) and cytoarchitectural atypia. It is benign/borderline or malignant according to the degree of dysplasia ± invasion (20–30% are associated with colloid or ductal adenocarcinoma). 80% are in the head of pancreas and multifocal within the duct system. It shows indolent behaviour marked by MUC 2 phenotype in distinction from the MUC 1 aggressive ductal phenotype of usual pancreatic cancer.

— serous macro/microcystic tumours:
elderly in the head or tail (50–75%) and mostly benign (microcystic/oligocystic serous adenoma) but occasionally malignant. It comprises glycogen-rich, clear cuboidal epithelium lining fluid-filled microcysts with a central scar. Diagnosis can be aided by analysis of aspirated cyst fluid which, in distinction from mucinous cystic tumours and pseudocysts, has low viscosity and zero levels of leucocyte esterase. Surgical excision is curative.

— mucinous cystic tumours:
benign/borderline/malignant spectrum of appearance and behaviour tending to malignancy. Prognosis relates to the degree of invasion (which can be focal within a lesion) into pancreatic and extrapancreatic tissues. The carcinoma is usually ductal in character, occasionally adenosquamous or pleomorphic/giant cell. In general, indolent growth with spread to abdominal cavity occurring in middle-aged women but 90–95% 5-year survival if completely excised. Uni-/multilocular, body/tail of pancreas and potentially resectable. Characteristic ovarian type stroma in the wall (helpful to distinguish from pancreatic pseudocyst when the epithelial lining is lost) and no connection to the duct system.

— solid-cystic-papillary tumour (syn. solid-pseudopapillary tumour):

adolescent girls/young women of low malignant potential but usually benign. It comprises pseudopapillae covered by several layers of uniform, endocrine-like epithelial cells and a vascularized, hyalinized stroma with necrosis and mucinous cystic change. Alpha-1-antitrypsin/vimentin/CD10 positive, ± neuroendocrine markers (chromogranin/CD56/synaptophysin), and cytokeratin negative.

— acinar cell carcinoma:
1–2% of cases in the head of pancreas and uniform cells with cytoplasmic granules resembling normal pancreas. Enzyme antibody positive, e.g. lipase, amylase, trypsin. Nodal and liver metastases can be present in 50% of cases at diagnosis and aggressive.

— mixed differentiation carcinoma:
acinar/endocrine or ductal/endocrine are rare and behave as for ductal carcinoma. The endocrine component must be at least 30 % of the tumour.

— small cell carcinoma:
presents at late stage, poor prognosis.

— pancreaticoblastoma:
malignant in children and favourable prognosis if resected before metastases (nodal/hepatic 35% of cases). Also chemoresponsive. Consists of epithelial (acini, squamous nests) and mesenchymal (spindle cell) components.

(b) Endocrine (islet cell tumours)

— arise from pluripotential ductal cells showing neuroendocrine differentiation.

— forming a minority of pancreatic neoplasms (1–5%) usually occurring in adults. Small (<1–2 cm), circumscribed and solid/trabecular/gyriform/glandular cell patterns with hyaline (±amyloid) stroma. The majority are benign insulinomas (80–90%). Prognosis depends on the functional subtype, adequacy of surgical excision and the extent of disease.

1. Functional hormonal syndrome (60–85%)
   gastrinoma: pancreatic head, duodenum, gastric antrum, Zollinger-Ellison syndrome (multiple gastroduodenal ulcers, carcinoid tumourlets or microadenomas).
   insulinoma: body and tail—psychiatric/neurological symptoms/hypoglycaemia.
   vipoma: body and tail—watery diarrhoea, hypocalcaemia and achlorhydria.
   glucagonoma: body and tail—diabetes mellitus/skin rash/stomatitis.
2. Non-functional
   somatostatinoma: also in the duodenum with a glandular pattern and psammoma bodies and must be distinguished from well-differentiated adenocarcinoma.
   Ppoma.
   neurotensinoma.

calcitoninoma.
small cell carcinoma: ± ectopic ACTH secretion, hypercalcaemia.

Cellular density, atypia, necrosis, mitoses (>2–10/10 hpfs) and a Ki-67 index >5% give some guide as to malignant potential but they are not reliable. Better indicators are:

— tumour type: insulinoma, 85–90% benign; gastrinoma, 60–85% malignant.
— size (>2–3 cm), site (e.g. duodenal) and invasion of vessels.
— unequivocal evidence of malignancy is gross invasion of adjacent organs, metastases to regional nodes, liver and other distant sites. Tumour growth is indolent and even patients with metastases can survive several years. Some respond to chemotherapy, e.g. streptozotocin. Occasional cases are of poorly differentiated high-grade small cell type.

Association with multiple endocrine neoplasia (MEN) syndrome. The pancreas is involved in 80–100% of type 1 MEN syndrome, gastrinoma being the commonest (50%) lesion. Associated abnormalities are hyperplasia or tumours of parathyroid, pituitary and adrenal glands.

(c) Mixed exocrine/endocrine carcinoma

— <1%; bivalent amphicrine cells or adjacent foci of mixed differentiation (the endocrine component being at least one-third of the tumour).

(d) Metastatic carcinoma

— direct spread: stomach, colorectum, biliary tract, abdominal mesothelioma/lymphoma.
— distant spread: pleomorphic carcinoma of the pancreas has to be distinguished from metastatic malignant melanoma, sarcoma, choriocarcinoma and large cell lung carcinoma. Small cell lung carcinoma and renal carcinoma.

It can be difficult to distinguish adenocarcinoma of the pancreas and adenocarcinoma of the terminal common bile duct from adenocarcinoma of the ampulla of Vater, as they can share similar histological features of biliary phenotype. Careful examination of the exact anatomical location is required and circumstantial evidence for a point of origin, e.g. an adenomatous lesion in the ampullary mucosa or dysplasia in the pancreatic/bile duct epithelium. Ampullary cancers tend to an intestinal phenotype and immunoprofile (CK7 negative/CK20 positive) and pancreatic cancers a ductal appearance and different immunoexpression (CK7 positive/CK20 positive). Sometimes the only conclusion can be adenocarcinoma of the pancreatico-ampullary-biliary region.

3. DIFFERENTIATION

Well/moderate/poor/undifferentiated, or, Grade 1 /2/3/4.

Pancreatic ductal and ampullary adenocarcinoma can be graded according to the percentage tumour gland formation (well/G1 >95%: moderate/G2 50–95%: poor/G3 <50%).

By convention and definition signet ring cell adenocarcinoma and undifferentiated carcinoma (no glandular differentiation) are grade 3 and grade 4, respectively. Well-differentiated pancreatic adenocarcinoma can be difficult to distinguish from non-neoplastic ducts. Malignant glands are of variable size, shape and angularity with atypical nuclear/nucleolar features. Cell cytoplasm is tall and pale to clear in character. Perineural invasion is diagnostically helpful.

Intraduct papillary lesions are:

Low-grade	mild nuclear atypia no mitoses
Intermediate	moderate nuclear atypia <5 mitoses/10 hpfs
High-grade	severe cellular atypia mitoses >5/10 hpfs

Endocrine tumours are not graded because of poor correlation of cytological features and growth pattern with biological behaviour.

4. EXTENT OF LOCAL TUMOUR SPREAD

Border: pushing/infiltrative.

Lymphocytic reaction: prominent/sparse.

The TNM classification applies to carcinomas of the ampulla of Vater and exocrine pancreas.

Ampulla

pTis	carcinoma in situ
pT1	tumour limited to the ampulla or sphincter of Oddi
pT2	tumour invades duodenal wall
pT3	tumour invades pancreas
pT4	tumour invades peripancreatic soft tissues or other adjacent organs or structures.

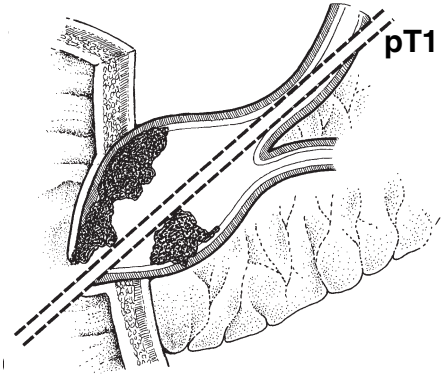


FIGURE 3.1. Ampulla of Vater carcinoma.

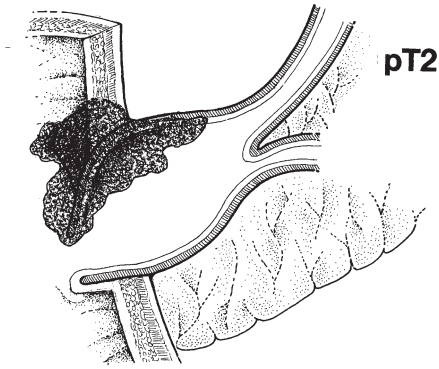


FIGURE 3.2. Ampulla of Vater carcinoma.

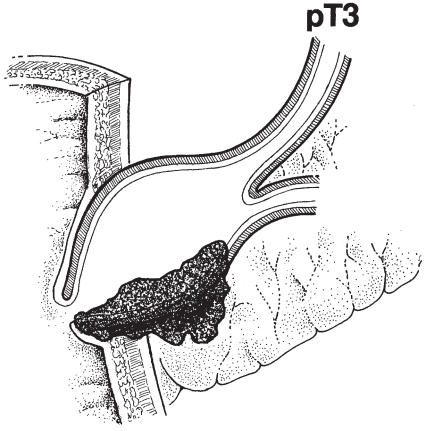


FIGURE 3.3. Ampulla of Vater carcinoma.

Pancreas

pTis	carcinoma in situ
pT1	tumour limited to the pancreas, ≤2 cm maximum dimension
pT2	tumour limited to the pancreas, >2 cm dimension
pT3	tumour extends beyond pancreas*, but without involvement of coeliac axis or superior mesenteric artery
pT4	tumour involves coeliac axis or superior mesenteric artery.

*Beyond pancreas includes the retroperitoneal fat and space, mesenteric fat, mesocolon, greater and lesser omenta and peritoneum. Direct invasion to bile ducts and duodenum includes involvement of the ampulla of Vater. Peripancreatic soft tissue involvement is an adverse prognostic indicator.

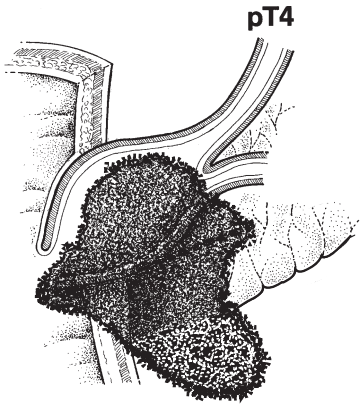


FIGURE 3.4. Ampulla of Vater carcinoma.

5. LYMPHOVASCULAR INVASION

Present/absent.
Intra-/extratumoral.

Perineural space involvement is common in pancreatic carcinoma and lymphovascular invasion is present in up to 50% of cases with spread to local regional nodes at the time of diagnosis. Invasion of portal vein has adverse independent prognostic significance. Sites of distant metastases are liver, peritoneum, lung, adrenal, bone, skin and CNS. Regional node involvement is also present in 35–50% of ampullary carcinomas.

6. LYMPH NODES

Site/number/size/number involved/limit node/extracapsular spread.
Regional nodes: peripancreatic, pancreaticoduodenal, common bile duct, pyloric and proximal mesenteric. A regional lymphadenectomy will ordinarily include a minimum of 10 lymph nodes.

pN0 no regional lymph node metastasis
pN1 metastasis in regional lymph node(s).

7. EXCISION MARGINS

Distances (mm) to the following margins; proximal (gastric/duodenal), distal (duodenal), common bile duct, distal pancreatic, posterior pancreatic surface (deep radial).

The commonest site for local recurrence of invasive carcinoma after a Whipple's procedure is the posterior pancreatic soft tissue margin. This should be inked accordingly and the distance of tumour to it measured. Similarly for the non-peritonealized margin of the uncinate process. Local recurrence from intraductal tumour is more likely at a ductal resection margin.

8. OTHER PATHOLOGY

Cholestatic jaundice—carcinoma head of pancreas and ampulla.

Ampulla

— duodenal adenoma(s), familial adenomatous polyposis coli (ampullary carcinoma is one of the commonest causes of death in FAPC).

Pancreas

— 3–10% of pancreatic carcinoma are familial—hereditary, BRCA2, HNPCC.
— disseminated intravascular coagulation, thrombophlebitis migrans (25% of cases, particularly with mucin-secreting tumours).
— gastrointestinal neuroendocrine syndromes, e.g. Zollinger-Ellison syndrome (diarrhoea, gastric hyperacidity with gastric/duodenal/jejunal ulcers), Werner-Morrison syndrome, WDHA syndrome (watery diarrhoea, hypokalaemia, alkalosis).
— chronic pancreatitis shows acinar atrophy, distortion and regenerative changes with stromal fibrosis and residual islet tissue and can mimic pancreatic carcinoma. Similar changes are also seen upstream and adjacent to pancreatic carcinoma due to duct obstruction indicating that interpretation and sampling can be problematic. Ductules in chronic pancreatitis tend to retain their lobular architecture, lack significant malignant cytological change and show no invasion of nerve sheaths or peripancreatic fat. Jaundice of short duration in a patient older than 60 years is suspicious of malignancy. Other indicators are elevated serum CA19-9 (usually in cancers >3 cm diame-

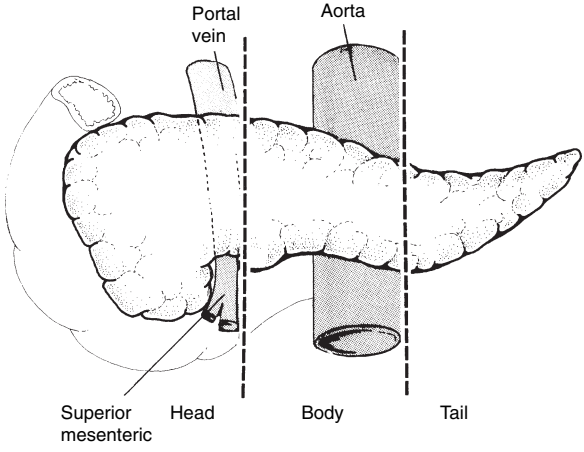


FIGURE 3.5. Pancreas.

ter), duct stricture at ERCP or a mass lesion on CT/ELUS. Imaging is important in establishing contraindications to surgery (distant nodal/major vessel involvement) or other potentially operable diagnoses, e.g. serous or mucinous cystic tumours. A tissue diagnosis may be obtained by positive duct cytology brushings or transduodenal/percutaneous FNA or needle core biopsy. This is important to exclude other treatable malignancies, e.g. lymphoma in peripancreatic nodes. In a proportion of cases a firm diagnosis will not be obtained and must be assumed on the basis of clinical probability. Thus pancreaticoduodenectomy has a 5% false negative rate on the basis of benign disease.

Immunophenotype

— neuroendocrine: chromogranin, synaptophysin, CD56.
— hormonal: specific peptides—insulin, glucagon, gastrin, pancreatic polypeptide, VIP, ACTH, somatostatin.
— exocrine carcinoma: cytokeratins (including CK7, CK8, CK18, CK19, ±CK20), CEA, CA19-9, CA-125, MUC I—expressed in >80% of ductal

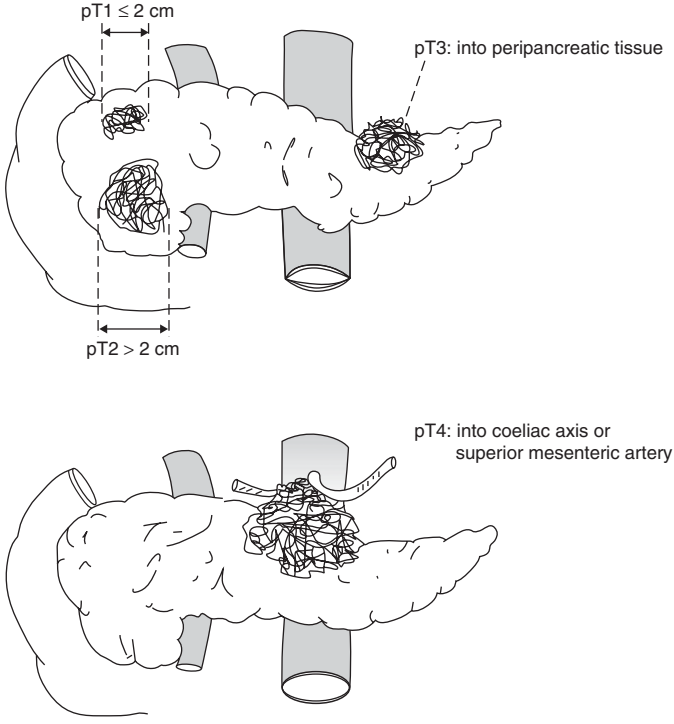


FIGURE 3.6. Pancreatic carcinoma.

lesions, ±CDX-2.

Prognosis

Prognosis in pancreatic ductal carcinoma is poor with most patients dead within several months. It relates to tumour site (body and tail are worse than head, as the latter may present early with obstructive jaundice), size (>4.5 cm is adverse), histological grade and stage. Overall 5-year survival is 2%, even disease confined to the pancreas only reaching 15%. There is limited suitability for resection (5–10% of cases), namely, node-negative tumours of the pancreatic head <3 cm diameter with no major (superior mesenteric or portal) vessel invasion. The majority present with advanced disease into lymph node and retroperitoneal tissues. Treatment is palliative with relief of ductal biliary obstruction by open or laparoscopic bypass or endoscopic stent insertion. Mucinous cystic tumours are less frequent but potentially resectable. Pancreatic endocrine tumours may present with their associated metabolic or gastrointestinal syndrome and have an indolent time course being of low- to intermediate-grade malignancy. Ampullary carcinoma is more favourable than pancreatic or bile duct carcinoma with a 5-year survival of 25–50%. This can improve to 80–85% if the tumour is at an early stage and confined to the sphincter of Oddi (pT1). Transduodenal wide local excision may be adequate for carefully selected ampullary tumours, e.g. adenoma, but only after careful staging and exclusion of an underlying mass lesion requiring radical surgery.

9. OTHER MALIGNANCY

Leukaemia

Lymphoma

— usually spread from para-aortic/peripancreatic nodal lymphoma.
— extramedullary plasmacytoma.

Sarcoma

— rare
— leiomyosarcoma, liposarcoma, fibrosarcoma, osteosarcoma.
— exclude secondary from gut (spindle cell carcinoma/GIST/sarcoma) or retroperitoneum.

4
Small Intestinal Carcinoma

1. GROSS DESCRIPTION

Specimen

— endoscopic/laparoscopic or open biopsy/resection. Whipple's pancreaticoduodenectomy, segmental bowel resection, right hemicolectomy: depending on the tumour site in the proximal/mid-/distal small bowel, respectively. Needle core biopsy of a small intestinal or mesenteric mass is usually avoided due to the risk of capsule rupture and tumour seeding jeopardizing complete primary resection, suitability for which is assessed by CT scan.
— weight (g) and size/length (cm), number of fragments.

Tumour

Site

— duodenum (particularly periampullary) 70%: see Chapter 3.
— jejunum/ileum 30%.
— mucous membrane/muscularis/extramural.
— serosal/mesenteric/nodal/single/multifocal.
— mesenteric/anti-mesenteric border.
— Meckel's diverticulum.

Size

— length × width × depth (cm) or maximum dimension (cm).

Appearance

— polypoid/sessile/ulcerated/diffusely infiltrative/fleshy/pigmented/yellow/stricture/intussusception ± secondary ischaemic necrosis of the tumour tip/intussusceptum or receiving segment (intussuscipiens).

Duodenal carcinomas tend to be papillary or polypoid, distal carcinoma ulcerated and annular with constriction of the bowel wall (napkin ring-like). Presentation can be non-specific, e.g. anaemia or weight loss, with poorly defined central abdominal pain or signs of subacute obstruction. There may be a detectable mass either on abdominal examination or CT scan. Carcinoid tumour is nodular, yellow, uni-/multifocal causing

bowel obstruction due to fibrosis or acting as the apex of an intussusception. Malignant lymphoma can be subtle in the edge of a perforated jejunitis or a fungating, fleshy mural or mesenteric mass. There may be a preceding history of coeliac disease. Metastases are often serosal seedlings, nodules or plaques. GISTs are mural lesions which can be dumb bell-shaped with luminal and extramural components. They can also be separate from the bowel and mesenteric in location.

Edge
— circumscribed/irregular.

2. HISTOLOGICAL TYPE

Adenocarcinoma
— enteric pattern, well or moderately differentiated: usual type.
— anaplastic (poorly differentiated) forms also occur more frequently than in colorectal cancer.
— mucinous carcinoma: >50% of the tumour area.
— signet ring cell carcinoma: >50 % of the tumour cells.

Diagnosis of primary small intestinal adenocarcinoma is by exclusion of spread from more common sites, e.g. colorectum and stomach. Similar to the large intestine there is some evidence for a dysplasia (adenoma)–carcinoma sequence in the adjacent mucosa. Prognosis is poor due to late presentation and advanced stage.

Carcinoid tumour
— yellow/nodular/±multifocal.
— chromogranin/synaptophysin/CD56 positive.
— typically insular pattern of uniform cells in a dense fibrous stroma with vascular thickening.
— 20% have carcinoid syndrome implying liver metastases: facial flushing/asthma/thickening of cardiac valves due to release of the vasoactive peptides (e.g. serotonin) into the systemic circulation.
— low-grade malignancy: any functioning well-differentiated tumour; any tumour with angioinvasion; non-functioning tumour ≥2 cm or with invasion beyond the submucosa.
— high-grade malignancy: tumour with a high mitotic rate, cellular atypia or necrosis and poorly differentiated tumours/small cell carcinomas.

Carcinoid tumour has an overall 5-year survival rate of 50–65%. It is better for small lesions [metastatic rate: <1 cm (2%), 1–2 cm (50%), >2 cm (80%)] confined to the wall (85%) than those invading the serosa or beyond (5%). Metastases are to regional nodes and liver (multiple, solid/cystic): also bone, skin and thyroid. The above comments relate mostly to classical EC cell jejuno-ileal carcinoids. Duodenal carcinoids have a better prognosis, occur mainly in D1/D2 and include non-functioning G cell tumours, gastrinomas (Zollinger Ellison/MEN syndromes), somatostatinoma and gangliocytic paraganglioma.

Others
— rare: adenosquamous, sarcomatoid carcinoma; aggressive.

Metastatic carcinoma
— direct spread: colorectum, ovary, stomach, pancreas.
— distant spread: lung, breast and choriocarcinoma.

The bulk of disease is extramural but tumour can invade muscularis and mucous membrane causing obstruction or perforation and mimicking a primary lesion. Adjacent mucosal dysplasia is a useful pointer and adenoma is present in 24% of primary lesions. Small bowel is a common site of metastatic malignancy with formation of peritoneal seedlings, multiple nodules, plaques and strictures causing obstruction.

Metastatic melanoma
— pigmented/multifocal.
— amelanotic/oligomelanotic.
— melanoma requires confirmation with S100, HMB-45, melan-A.

3. DIFFERENTIATION
Adenocarcinoma: well/moderate/poor/undifferentiated, or Grade 1/2/3/4 based on the percentage tumour gland formation (well/G1 >95%: moderate/G2 50–95%: poor/G3 <50%). Signet ring cell carcinoma is grade 3, small cell and undifferentiated carcinoma (no gland formation) grade 4.
Lymphoma: low-/high-grade based on the number of blast cells present.
Sarcoma: low-/high-grade based on the degree of cellularity, atypia, necrosis and mitoses.

4. EXTENT OF LOCAL TUMOUR SPREAD
Border: pushing/infiltrative.
Lymphocytic reaction: prominent/sparse.
The TMN classification applies only to carcinoma:

pTis	carcinoma in situ
pT1	tumour invades lamina propria or submucosa
pT2	tumour invades muscularis propria
pT3	tumour invades through muscularis propria into subserosa or into non-peritonealized perimuscular tissue (mesentery or retroperitoneum) with extension ≤2 cm
pT4	tumour perforates visceral peritoneum or directly invades other organs/structures (including loops of small intestine, mesentery, retroperitoneum >2 cm and abdominal wall via serosa; also for duodenum—invasion of pancreas).

The non-peritonealised perimuscular tissue is, for jejunum and ileum, part of the mesentery and, for duodenum in areas where serosa is lacking, part of the retroperitoneum.

5. LYMPHOVASCULAR INVASION
Present/absent.
Intra-/extratumoral.

Vessel wall fibrosis/stenosis in carcinoid tumour.
Metastatic carcinoma often shows quite extensive lymphovascular invasion in the various layers of the bowel wall.

6. LYMPH NODES

Site/number/size/number involved/limit node/extracapsular spread.
Regional nodes: duodenum—gastroduodenal, pancreaticoduodenal, pyloric, hepatic, superior mesenteric; ileum/jejunum—mesenteric; terminal ileum—ileocolic, posterior caecal. A regional lymphadenectomy will ordinarily include a minimum of six lymph nodes.

pN0 no regional lymph node metastasis
pN1 metastasis in regional lymph node(s)

7. EXCISION MARGINS

Distances (mm) to the nearest longitudinal limit of resection and painted deep radial (non-peritonealized soft tissue) mesenteric margin. In a segmental bowel resection it is usual to clear a 5-cm length of intestine on either side of the tumour with en bloc resection of a wedge of mesentery.

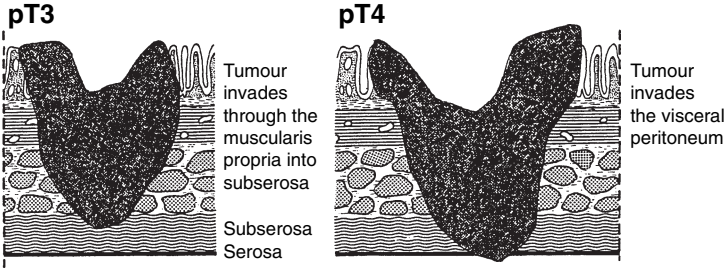


FIGURE 4.1. Small intestinal carcinoma.

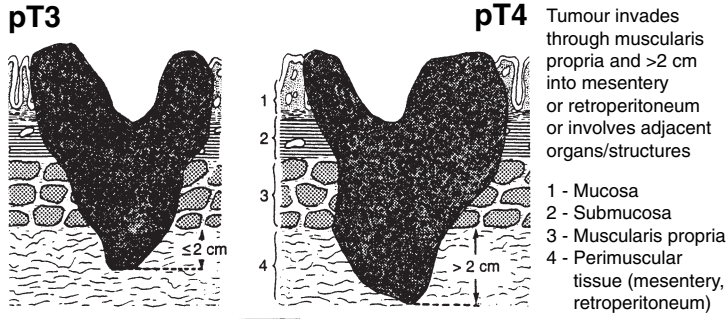


FIGURE 4.2. Small intestinal carcinoma.

8. OTHER PATHOLOGY

There is increased incidence of adenocarcinoma in:

— familial adenomatous polyposis coli, particularly periampullary related to duodenal adenomas. It is a significant cause of mortality in FAPC
— hereditary non-polyposis colon cancer
— Peutz–Jegher's polyposis (beware epithelial misplacement/pseudo-invasion); rare
— Crohn's disease
— coeliac disease
— ileostomy
— Meckel's diverticulum: rare—also carcinoid tumour, GIST, leiomyosarcoma

Coeliac disease/ulcerative jejunitis/gluten-induced intestinal or enteropathy-associated T cell lymphoma (EATCL): change in or lack of responsiveness to a gluten-free diet or presentation as an ulcerative/perforated jejunitis or an abdominal mass in an older patient can indicate onset of EATCL.
Stricture—carcinoid, metastases.
Intussusception—carcinoid, lymphoma.
Multifocal—carcinoid, lymphoma, malignant melanoma, metastases.
Meckel's diverticulum—carcinoid, adenocarcinoma, leiomyomatous tumours.

Immunophenotype

Small bowel adenocarcinoma is CAM5.2, AE1/AE3, CEA, CK20, CDX-2 positive. About 50% are also CK7 positive.

Prognosis

Small bowel adenocarcinoma is unusual, being 50 times less common than large bowel carcinoma. Seventy percent occur in the duodenum, particularly the periampullary region. Presentation is late due to the fluid content of the bowel. Many patients already have transmural spread and lymph node metastases and the majority subsequently die from their disease. Five-year survival rates are approximately 10–20% with the most important prognostic indicator being depth of spread or stage of disease. Surgical resection is the treatment of choice.

9. OTHER MALIGNANCY

Lymphoma

— single or multifocal, primary or secondary to nodal/systemic disease. Primary disease centres on the bowel with or without spread to regional nodes.
— MALToma:
low/high-grade
B cell (70–90% of bowel lymphomas)

centrocyte-like cells with variable numbers of blasts (>20% = high-grade)
lymphoepithelial lesions
monotypic immunoglobulin expression
±eosinophilia
high-grade lesions are on a spectrum with diffuse large B-cell lymphoma.
— Burkitt's-type/B-lymphoblastic:
children (or adults with AIDS, non-endemic/non-EBV related)
terminal ileum/ileocaecal valve—a high-grade lymphoma
CD20, CD10, CD79a, tdt positive (lymphoblastic lymphoma). High (>90%) Ki67 index, starry sky appearance.
— multiple lymphomatous polyposis:
centrocytic lymphoma or mantle cell lymphoma—splenic, small and large bowel disease with numerous intestinal polyps
an intermediate-grade lymphoma—aggressive disease with advanced stage at presentation
CD20, CD5, cyclin D1 positive.
— EATCL: aggressive. 5% of GI lymphomas. Proximal jejunum. Pleomorphic medium to large cell infiltrate (CD3 positive) and adjacent enteropathic mucosa (atrophy/increased intraepithelial lymphocytes).
— follicle centre cell (follicular) lymphoma:
more usually spread from nodal disease rather than primary.
— immunoproliferative small intestinal disease (IPSID):
Mediterranean countries
alpha chain disease.
— post-transplant lymphoproliferative disorders:
polyclonal/monclonal/disparate morphology and behaviour
some regress on decreasing immunosuppression therapy, e.g. cyclosporin (see Chapter 35).

Prognosis is better for low-grade B cell lymphomas (44–75% 5-year survival) than high-grade B- or T-cell lymphomas (25–37% 5-year survival). Adverse prognostic indicators are perforation, high-grade histology, multiple tumours, large size, serosal penetration and advanced stage (Ann Arbor System, see Chapter 35).

Gastrointestinal mesenchymal and stromal tumours (GISTs)
— spindle cells, epithelioid cells, skeinoid collagen fibres. Note also that extraintestinal mesenteric or retroperitoneal lesions can occur.
— ileum 50%, jejunum 40%, duodenum 10%.

Myogenic: 10%—desmin/h-caldesmon/smooth muscle actin positive and c-kit negative. True leiomyoma or leiomyosarcoma.

Neural: 2–5%—S100/synaptophysin positive and c-kit negative. Schwannoma, neurofibroma (can be associated with von Recklinghausen's disease/MEN syndrome and GISTs elsewhere in the gut).

Stromal: CD34 and CD117 (c-*kit*:tyrosine kinase receptor) positive, with absent or incomplete myogenic/neural differentiation. Putative precur-

sors are the interstitial cells of Cajal, which are gut pacemaker cells located in the deep submucosa and myenteric plexus. Note that there can be marked heterogeneity and focal expression of antigens. In general, antigen positivity is CD117 (95%), CD34 (70–85%), smooth muscle actin (20-40%), h-caldesmon (60–80%) and nestin (90–100%). C-kit-negative GISTs may be identified by positive protein kinase c theta and PDGFR. Note that other malignant tumours can also be c-kit positive, e.g. seminoma, melanoma and some metastatic carcinomas, e.g. breast, ovary, colorectal, small cell carcinoma. GANT is now regarded as a variant of GIST and assessed accordingly.

Malignancy relates to: size (>2–5 cm), cellularity, atypia, cell type (epithelioid is worse than spindle cell), necrosis, margins and mitoses. Prognosis (approximately 50% 5-year survival) is also stage dependent.

DNA ploidy, Ki-67 proliferation indices (>10%), overexpression of p53, loss of CD34 and CD117 immunoexpression and morphometry also correlate with these parameters.

Lesions are NIH categorized as being very low, low, intermediate or high metastatic risk on the basis of size and mitoses (see Table 2.2).

Prognosis in gastrointestinal stromal tumours is dependent on patient age, tumour size (>5 cm), tumour site and mitotic activity. A robust criterion in stomach tumours is >5 mitoses/50 hpfs, but mid- and hindgut lesions are more aggressive (even if <5 cm diameter and mitotic counts are low) than foregut tumours. Behaviour can also be unpredictable, with clinicopathological factors at best being only broadly indicative, and the terminology "gastrointestinal stromal tumour of uncertain malignant potential" is useful. With an established diagnosis of sarcoma histological grading is not a reliable index of metastatic potential and tumour size is a better indicator. So much so that a proposed TNM staging system is pT1 <5 cm diameter, pT2 >5 cm diameter. Metastases are commonly to peritoneum, liver, pancreas, retroperitoneum and lungs. Metastatic disease responds well to STI 57I (Glivec, Imatinib) agent giving several disease-free years, but usually therapeutic escape occurs with recurrent peritoneal disease. This may relate to new acquired genetic mutations in the tumour cells.

Kaposi's sarcoma

— AIDS: 50% of high-risk patients have visceral involvement.

Leukaemia

— 14.8–25% of cases.
— granulocytic sarcoma (CD68/chloroacetate esterase positive).

5
Colorectal Carcinoma

1. GROSS DESCRIPTION

Specimen

— investigation of colorectal cancer is by endoscopy and biopsy with staging of biopsy-proven cancers by CT scan of chest, abdomen and pelvis for local and distant spread. MRI of rectal cancers complements clinical examination by imparting information about nodal disease and the status of the tumour edge in relation to the mesorectal envelope and its fascial plane, that influences neoadjuvant and operative management decisions.
— rectal/sigmoidoscopic/colonoscopic biopsy, right or left hemi-/transverse/sigmoid/ subtotal or total colectomy/anterior or abdominoperineal resection.
— weight (g) and size/length (cm), number of fragments. Curative colorectal cancer surgery excises the primary lesion with adequate longitudinal and deep radial margins and en bloc resection of the relevant colonic lymphovascular mesenteric pedicle, or the mesorectum.

Tumour

Site

— caecum/ascending colon/hepatic flexure/transverse colon/splenic flexure/descending or sigmoid colon/rectum/multifocal (10%—synchronous or metachronous). Rectosigmoid (50%) are the commonest sites. Tumour site strongly influences clinical presentation, e.g. caecal carcinoma—anaemia, right iliac fossa mass; sigmoid colon carcinoma—alteration in bowel habit; rectal cancer—bright red blood per rectum, tenesmus.
— for rectum: above/at/below the peritoneal reflection. Tumours below the reflection have a higher rate of local recurrence and tumours above/at the reflection anteriorly may involve peritoneum. The lateral angled descent of the peritoneum results in variation of the anatomical relationships with the upper rectum orientated to mesorectum posteriorly and laterally and peritoneum anteriorly. The mid rectum is surrounded by mesorectum, whereas the lower rectum is below the level of

the mesorectum encircled by pelvic sphincteric and levator muscle. Elsewhere in the colorectum the bowel is orientated to serosa and a mesentery but the proximal ascending and descending colons and rectosigmoid junction have a posterior non-peritonealized retroperitoneal bare area. As in the mesorectum, this constitutes a deep radial soft tissue resection margin, although this can be difficult to identify in individual cases. Sigmoid colon ends where the external longitudinal muscle bands (taeniae coli) blend with the rectal muscularis propria.

— distances (cm) to the dentate line and nearest longitudinal resection limit. These figures can audit the rates of anterior resection versus abdominoperineal resection, with the former being the operation of choice (with total mesorectal excision: TME) for mid- and upper rectal cancers. Low rectal cancers also have higher local recurrence rates. Anatomical definition of the rectum varies but, in general, distances from the anal verge are: lower rectum 0–5 cm; mid rectum 5–10 cm; upper rectum 10–15 cm. Tumour site within the rectum not only influences the choice of operative procedure but also neoadjuvant therapy, e.g. low rectal cancers may be given long course as opposed to short course preoperative radiotherapy. A further important audit factor is the integrity or completeness of the mesorectal envelope in the postoperative specimen. Deficiencies indicate a suboptimal operation and greater potential for local pelvic recurrence. A suggested classification is Quirke 1 (incomplete), 2 (nearly complete) and 3 (complete). Categories 1 and 2 show variable mesorectal bulk and deficiencies or cuts into the mesorectal capsule but it is smooth and intact in category 3.

Size

— length × width × depth (cm) or maximum luminal dimension (cm).

Not shown to be an independent prognostic indicator.

Appearance

— polypoid/annular/ulcerated/mucoid/linitis plastica/stricture/plaque.

No independent influence on prognosis except linitis plastica (signet ring cell carcinoma). Proximal cancers tend to be exophytic masses, other sites ulcerated, endophytic and annular.

Edge

— circumscribed/irregular.

Perforation

— present/absent. Perforation has a higher incidence of local recurrence and poorer prognosis. Perforation through the tumour is TNM stage pT4 because of the potential contact with peritoneum. This does not include proximal ischaemic back-pressure perforation (e.g. caecum) due to an obstructing distal cancer. In this case the pT stage is determined by the degree of local spread of the distal cancer.

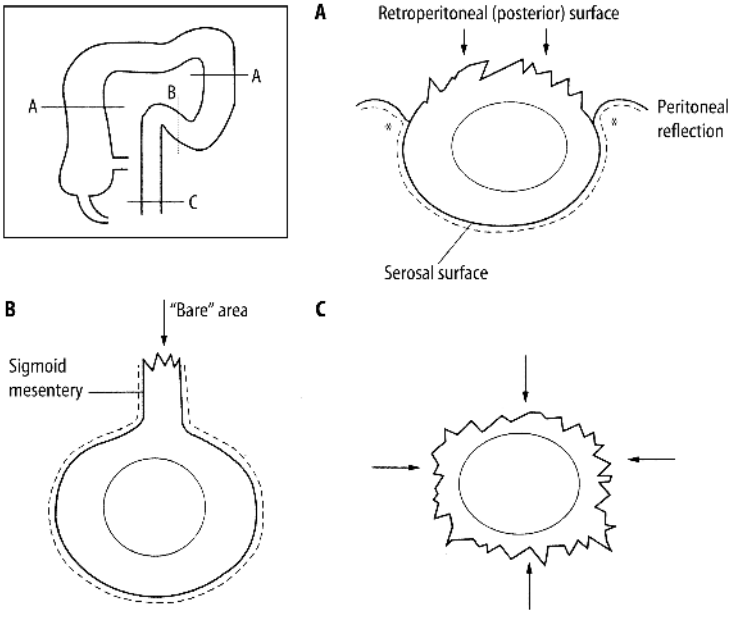


FIGURE 5.1. Extent of serosal covering of the large intestine. Arrows indicate the "bare" non-peritonealized areas of different levels. A. The ascending and descending colon are devoid of peritoneum on their posterior surface. B. The sigmoid colon is completely covered with peritoneum, which extends over the mesentery. C. The lower rectum lies beneath the pelvic peritoneal reflection. The asterisks in A indicate the sites where serosal involvement by tumour is likely to occur. (Reproduced with permission from Burroughs SH, Williams GT. ACP best practice no. 159. Examination of large-intestine resection specimens. J Clin Pathol 2000;53:345, reproduced with permission from the BMJ Publishing Group.)

2. HISTOLOGICAL TYPE

Adenocarcinoma, no specific type (NST)

— 85% of cases.
— diagnostic criteria are: (a) malignant epithelial changes, in (b) a desmoplastic stroma, with (c) invasion beneath the muscularis mucosae. In practice a combination of (a) and (b) is the most useful.

Mucinous carcinoma

— 10% of cases.
— tumour area >50% mucinous component.
— worse prognosis (5-year survival decreased by 10–15%) compared with an equivalent-stage adenocarcinoma, NST, although this remains controversial.

Signet ring cell adenocarcinoma
— >50% signet ring cells.
— poor prognosis in the rectosigmoid of young or elderly people with a linitis plastica pattern of annular thickening and stenosis.
— distinguish from secondary carcinoma, e.g. gastric signet ring cell carcinoma in young females, prostate carcinoma [prostate-specific antigen (PSA) positive] in older males.

Others
— neuroendocrine carcinoma:
carcinoid/large cell/small cell (right colon, prognosis poor)
— adenocarcinoid:
composite adenocarcinoma and carcinoid
— adenosquamous carcinoma:
caecum
— squamous cell carcinoma:
rectal: can be seen in ulcerative colitis/schistosomiasis/amoebiasis. Exclude spread from an anal carcinoma or cervical carcinoma. Need intercellular bridges ± keratinization with no gland/mucin formation
— undifferentiated carcinoma:
(a) good prognosis—medullary carcinoma. Circumscribed and expansile margin with solid sheets of tumour cells, intra- and peritumoral lymphocytes. Sporadic or in HNPCC and strongly associated with MSI-H (see below)
(b) poor prognosis—pleomorphic and diffusely infiltrative
— mixed differentiation:
e.g. adenocarcinoma (NST) with small cell carcinoma.
— metastatic carcinoma:
transcoelomic spread: stomach, ovary, endometrium, gut, pancreas
direct spread: prostate, anus, cervix, kidney
distant spread: breast (infiltrating lobular), malignant melanoma, lung
Metastatic disease can infiltrate bowel wall and protrude into the mucosa mimicking endoscopically and macroscopically a primary lesion—a relevant previous history is crucial to diagnosis.

3. DIFFERENTIATION
Well/moderate/poor/undifferentiated, or, Grade 1/2/3/4 based on the percentage tumour gland formation (well/G1 >95%; moderate/G2 50–95%; poor/G3 <50%).

Undifferentiated carcinoma (grade 4) shows no gland formation.

Low-grade or high-grade: due to the difference in prognosis a two-tiered grading system is recommended with low-grade (well/moderately differentiated) and high-grade (poor/undifferentiated). Signet ring cell (grade 3), small cell and undifferentiated carcinomas (both grade 4) are high-grade cancers.

— 70–80% are moderately differentiated.
— based on the predominant area and not the tumour margins, which can often show poorly differentiated microscopic foci. If there is a substan-

tial component of poor differentiation this should be commented upon. Some authors suggest that a poorly differentiated invasive margin (with budding, microacini and undifferentiated cells) in an otherwise moderately differentiated tumour is predictive of nodal metastases.

4. EXTENT OF LOCAL TUMOUR SPREAD

Border: pushing/infiltrative.
Lymphocytic reaction: prominent/sparse.
An expanding growth pattern/margin with a Crohn's-like inflammatory response is a better prognostic indicator than an infiltrating, irregular margin with no inflammation.
Degree of mesorectal/mesocolic spread from the outer border of the muscularis propria (>5 mm) seems to influence prognosis but is not well established.

When the mesocolic or mesorectal circumferential radial margin is involved the degree of tumour spread is an indicator of either advanced disease or alternatively inadequate surgery.

The TNM classification applies only to carcinomas.

pTis	carcinoma in situ: intraepithelial (within basement membrane) or invasion of lamina propria (intramucosal) with no extension through muscularis mucosae into submucosa
pT1	tumour invades submucosa
pT2	tumour invades muscularis propria
pT3	tumour invades beyond muscularis propria into subserosa or non-peritonealized pericolic/perirectal tissues
pT4	tumour invades the serosal surface or adjacent organs and/or perforation of visceral peritoneum*.

Serosal involvement is tumour either at or ulcerating the serosal surface as this is prognostically worse than tumour in a subserosal inflammatory reaction—about 10% of patients develop peritoneal or ovarian (Krükenberg) deposits and there is a higher rate of distant metastases than in direct invasion of adjacent organs or structures alone. Serosal pT4 disease may include direct involvement of other segments of colon, e.g. sigmoid colon by a caecal carcinoma. If no tumour is present in adhesions to other structures, e.g. bladder, classify as pT3. Separate omental deposits are metastatic (pM1) disease.

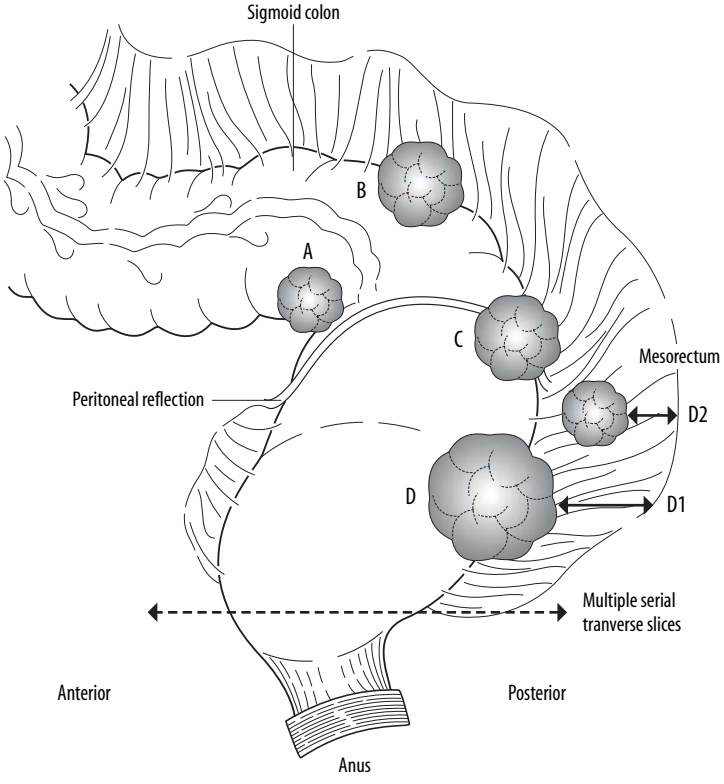
In low rectal cancer involvement of sphincteric muscle is pT3 and levator ani muscle is pT4.

Intramural extension to adjacent bowel, e.g. caecal carcinoma to ileum, does not affect the pT stage.

A minimum of five blocks of tumour and bowel wall is necessary to assess the pT stage adequately and to find extramural vascular invasion. The specimen is cut into serial transverse slices 4–5 mm thick, laid out in order and relevant slices selected for blocking.

Multiple carcinomas should be assessed and staged individually.

*Optional descriptors: pT4a (other organs/structures), pT4b (visceral peritoneum).



The upper anterior rectum is invested in peritoneum
The anterior mesorectum is thinner (0.75 - 1 cm) than the posterior mesorectum (1.5 - 3 cm)
Cut the resection specimen into multiple serial transverse slices about 5 mm thick
Blocks for histology are:

Above the reflection	A	tumour, rectal wall and serosa
	B	tumour, rectal wall and serosa
		tumour, rectal wall and mesentery
At the reflection	C	tumour, rectal wall and serosa
		tumour, rectal wall and mesorectum
Below the reflection	D	tumour, rectal wall and mesorectum
	D1	distance (mm) of the deepest point of continuous tumour extension to the nearest point of the painted CRM
	D2	distance (mm) of the deepest point of discontinous tumour extension (or in a lymphatic, node or vessel) to the nearest point of the painted CRM

FIGURE 5.2. Rectal carcinoma.

Direct implantation spread can be seen at anastomoses, peritoneal and abdominal wall wounds. Anastomotic site recurrence is unusual if the longitudinal margin clearance in the primary specimen is >5 cm.

5. LYMPHOVASCULAR INVASION

Present/absent.
Intra-/extratumoral.

Extramural venous invasion is an adverse prognostic factor: 35% 5-year survival. Often it comprises a tumour-filled longitudinal structure perpendicular to the muscularis propria and with some smooth muscle fibres in its wall. Adjacent "widowed" small arteries and an elastin stain can help identification. The significance of mural lymphovascular invasion is uncertain but should be reported as distinction between lymphatic and small venules can be difficult.

6. LYMPH NODES

Lymph nodes and liver are the commonest sites of metastases. Also peritoneum, lung, and ovaries and bladder where the metastases can mimic primary carcinoma of those organs. Immunophenotypical profiles may aid distinction, e.g. ovarian cancer is cytokeratin 7 positive/20 variable and weak for CEA, whereas gut cancer is strongly CEA positive and cytokeratin 7 negative/20 positive. Occasional colorectal cancers express CK7 and a minority are CK20 negative, particularly those with a high level of microsatellite instability, e.g. HNPCC.

Site/number/size/number involved/limit node/extracapsular spread.

Regional nodes: pericolic, perirectal, those located along the ileocolic, colic, inferior mesenteric, superior rectal and internal iliac arteries. A regional lymphadenectomy will ordinarily include a minimum of 12 lymph nodes. Lymph node yield varies greatly even after careful dissection. It is related to variation in individual anatomy, site (mesorectum yields few nodes), the extent of resection performed, and history of preoperative adjuvant therapy. External iliac, common iliac and superior mesenteric artery nodes are distant metastases.

pN0	no regional lymph node metastasis
pN1	1–3 involved regional lymph nodes
pN2	4 or more involved regional lymph nodes
Dukes' C1	nodes involved but apical node negative
Dukes' C2	suture tie limit apical node positive.

All regional lymph nodes should be sampled for histology:

— a minimum target of eight will identify the vast majority of Dukes' C lesions. Recent data recommend 10 as a minimum and that finding more than 15 does not confer additional benefit, although this is not universally accepted.
— remember to assess the small lymph nodes seen on histology adjacent to the tumour margin. The biological significance of nodal micrometastases (≤0.2 cm) is uncertain.

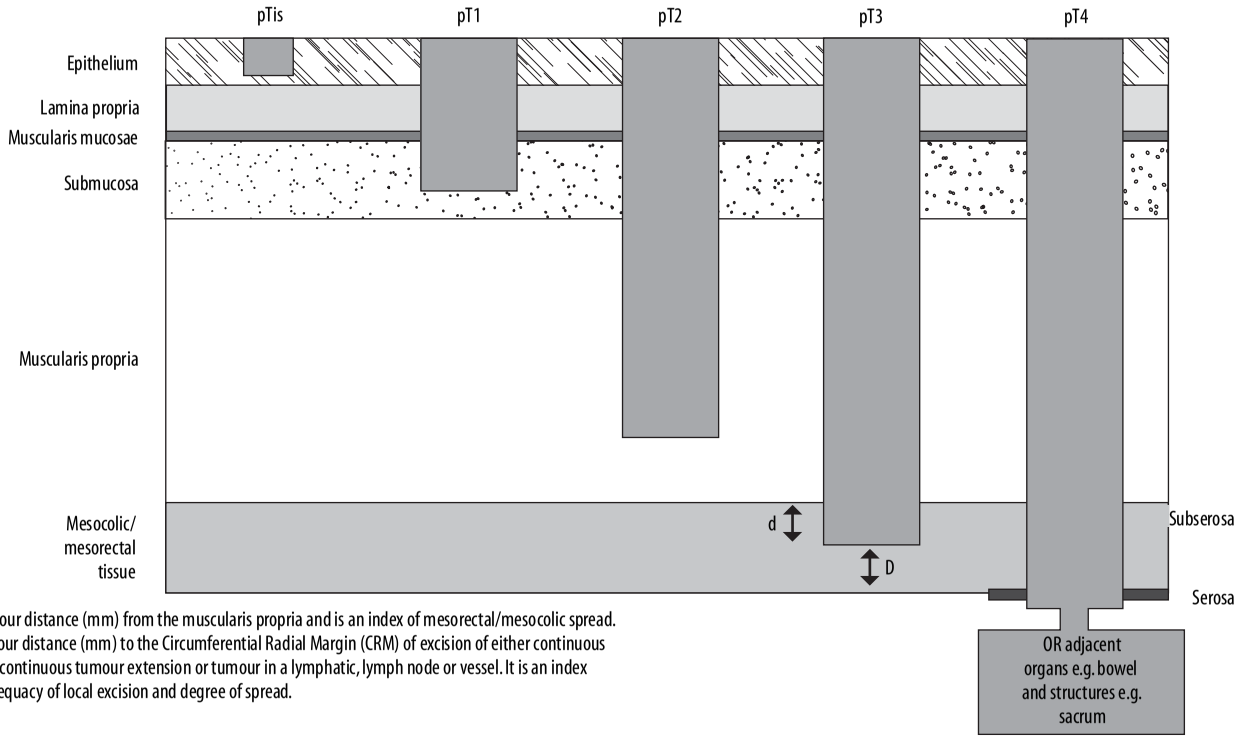


FIGURE 5.3. Colorectal carcinoma.

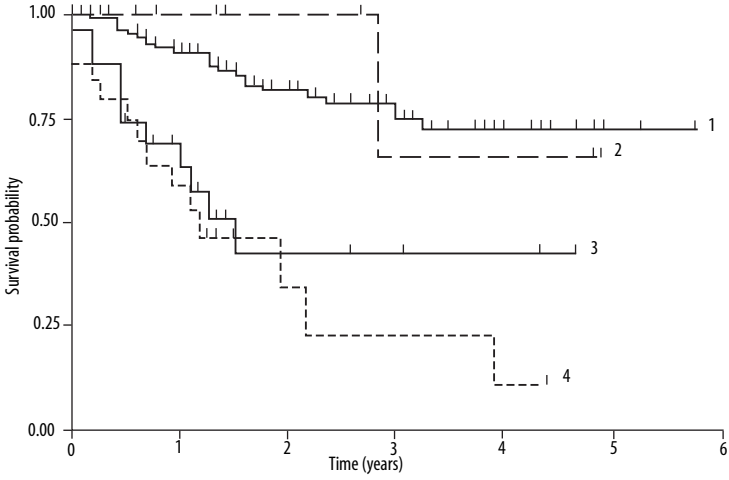


FIGURE 5.4. Kaplan-Meier cumulative survival curve for pertoneal involvement (Shepherd NA, Baxter KJ, Love SB. Influence of local peritoneal involvement on pelvic recurrence and prognosis in rectal cancer. J Clin Pathol 1995;48:849–855. Reproduced with permission from the BMJ Publishing Group). *Group 1*, tumour well clear of the closest peritoneal surface; *group 2*, mesothelial inflammatory/hyperplastic reaction with tumour close to but not actually at the peritoneal surface; *group 3*, tumour present at the peritoneal surface with inflammatory reaction/mesothelial hyperplasia/"ulceration"; *group 4*, tumour cells free in peritoneum and adjacent "ulceration".

— comment if an involved lymph node lies adjacent to (≤1 mm) the mesorectal CRM (circumferential radial margin) or mesocolic margin as this equates to involvement of that margin.
— direct invasion into a node is regarded as a nodal metastasis.
— a tumour nodule >3 mm in diameter in the perirectal/pericolic fat without evidence of residual lymph node is classified as a replaced nodal metastasis. If ≤3 mm diameter classify as discontinuous extension, i.e. pT3. It is important to note that this is a 5th edition TNM rule. The 6th edition TNM rule, which probably more accurately reflects biological events, is: a tumour nodule in the pericolic/perirectal adipose tissue without histological evidence of residual lymph node in the nodule is a lymph node metastasis if the nodule has the form and smooth contour of a lymph node. If of irregular contour it is classified as discontinuous pT3 spread and also as microscopic (V1) or macroscopic (V2) venous invasion as this is its likely origin. In the UK the Royal College of Pathologists has recommended using TMN 5 rather than TMN 6 due to concerns over the validity of ongoing clinical trials and the observer reproducibility in applying TNM 6. The resolution of this issue awaits further studies. In either case it should be ensured that the nodule does not represent tumour in an identifi-

able extramural vein and in practice pathologists often use a combination of these rules.
— more than one vascular pedicle suture tie may mean more than one apical node needs to be identified as such.

7. EXCISION MARGINS

Doughnuts/anastomotic rings/staple gun transections—involved/not involved.
Distances to the: nearest longitudinal resection limit (mm); mesorectal CRM (mm); mesocolic resection margin (mm).

Longitudinal spread beyond the gross edge of a colorectal carcinoma is unusual (<5% of cases) and anterior resection of rectal carcinoma is generally considered satisfactory if a macroscopic clearance of 2–3 cm beyond the lesion edge is feasible.

Block the nearest longitudinal surgical margin if ≤3 cm from the tumour edge, or if >3 cm but with any of: an unusually infiltrative tumour margin, extensive lymphovascular or mesorectal invasion or morphology such as signet ring cell, small cell, undifferentiated carcinoma.

CRM involvement = direct or discontinuous tumour spread, or tumour within a lymphatic, node or vessel ≤1 mm from the painted margin. Distances to this margin are best assessed using transverse serial slices of the resection specimen. Note that non-peritonealized CRMs exist not only in the mesorectum but also where the superior mesorectum joins the inferior aspect of the sigmoid mesentery, and in relation to the posterior aspects of the proximal ascending colon and descending colon.

The prognostic significance of mesocolic margin involvement has not been fully clarified but is clearly an index of spread of disease and/or adequacy of surgery.

8. OTHER PATHOLOGY

Predisposing conditions

Inflammatory: ulcerative colitis/Crohn's disease (1% of colorectal carcinoma), schistosomiasis, juvenile polyposis syndrome (10% risk). Carcinoma in ulcerative colitis occurs in patients with quiescent disease of pancolic distribution and long duration (>10–20 years). It may be associated with preceding or concurrent mucosal dysplasia above, adjacent to or distant from the tumour. A rectosigmoid biopsy positive for mucosal dysplasia is an indicator of the possible presence of carcinoma somewhere in the colorectum. Carcinomas may be multiple, right-sided and in up to one-third of cases difficult to define on endoscopic and gross examination. This is due to aberrant growth patterns with tumour arising in polypoid, villous or flat mucosal dysplasia in a background of mucosa already distorted by the effects of chronic inflammation, e.g. inflammatory polyps and strictures. Therefore interval colonoscopic biopsy of flat mucosa and target biopsy of possible DALMs (dysplasia associated lesion or mass) is employed to detect dysplasia as a marker of potential carcinoma which may be occult and submucosal in location. Due to variation

in observer reproducibility, mucosal dysplasia should be assessed by two experienced pathologists according to Riddell and/or the Vienna classification. In the absence of a DALM low-grade dysplasia may be followed up by colonoscopy, whereas persistent low-grade dysplasia, DALM-associated dysplasia or high-grade dysplasia should be considered for colectomy. Surface overexpression of Ki-67 and p53 is usual in a high-grade dysplasia and may help to distinguish from florid regenerative changes. Distinction from a sporadic adenoma in a colitic patent is usually made by the absence of dysplasia in the flat mucosa adjacent to and away from the lesion. Prognosis is variable as some lesions present late masked by the symptoms of ulcerative colitis and others are found early at regular (annual/biennial after 8–10 years' disease duration) surveillance colonoscopy.

Neoplastic: aberrant crypt foci (adenomatous, or, serrated ± dysplasia), adenoma(s), familial adenomatous polyposis coli (and the related Gardner's syndrome), previous or synchronous carcinoma(s), HNPCC (see below), hyperplastic polyposis (rare).

The usual dysplasia–carcinoma sequence indicates that development of adenocarcinoma increases with the size of adenoma, its degree of villous architecture and grade of dysplasia, multiplicity of lesions and age of the patient. A maximum diameter >2 cm and villous morphology confer approximate cancer risks of 50% and 40%, respectively. These risk factors in a rectal adenoma are also good indicators in individual patients for full colonoscopic survey and follow-up to detect right-sided colonic neoplasms.

In the UK severe or high-grade dysplasia is applied to epithelial proliferation of any degree of complexity that is mucosa based, i.e. above the muscularis mucosae. Adenocarcinoma is reserved for those lesions that show invasion below the muscularis mucosae. Terms such as carcinoma in situ tend to be avoided due to the relative lack of mucosal lymphatics, the rarity of nodal metastases with such lesions and the fear of over-treatment with unnecessary radical resection. However, it is not always possible to demonstrate invasion through the muscularis mucosae on biopsy and malignant epithelial changes with a desmoplastic stromal response are sufficient for a designation of adenocarcinoma. Sampling error must always be borne in mind in that a dysplastic fragment may not show the adjacent invasive component. Undoubtedly there are also malignant polyps for which terminology such as carcinoma in situ or intramucosal carcinoma is appropriate. In these circumstances there should be active discussion with the surgeon, emphasizing that the process is "mucosa-confined" and comments made on the adequacy of local excision. It should also be checked that the specimen is a complete polypectomy and not simply a diagnostic biopsy from the edge of a larger lesion.

Malignant polyps

Therapeutic polypectomy if the adenocarcinoma is:

(a) well or moderately differentiated
(b) clear of the stalk base
(c) without lymphovascular invasion.

Resection if the adenocarcinoma is:

(a) poorly differentiated (22%)*
(b) at (≤1 mm) the stalk base (11%)*
(c) shows lymphovascular invasion (18%)*.

Resection is more likely if the patient is young and medically fit to obviate the risk of nodal metastases which can occasionally occur with pT1 lesions (4%). A not uncommon finding is stalked adenomas in the sigmoid colon that twist and prolapse, resulting in glandular herniation into submucosa mimicking invasive carcinoma—the presence of haemosiderin, lack of stromal desmoplasia, surrounding lamina propria and cytoarchitectural abnormalities similar to those of the overlying adenoma are helpful pointers to a benign lesion.

Sessile adenomas with invasion: resection is indicated as this represents invasion of actual mural submucosa (Haggitt level 4) rather than just stalk submucosa (Haggitt levels 1, 2 and 3). Local transanal resection is considered for the very elderly and medically unfit. Indications for more radical surgery are: a lesion >3 cm diameter, incomplete tumour excision, deep submucosal (sm 3) or muscularis propria invasion, lymphovascular invasion or the presence of a poorly differentiated invasive component.

Flat adenomas: uncommon with a different genetic basis from usual adenomas and difficult to identify endoscopically on gross examination without magnification and dye spray techniques. Defined as up to twice the height of the adjacent mucosa with a height usually less than half its diameter (<10 mm across)—proportionately (×10 risk) higher grades of dysplasia and frequency of carcinoma. Depressed variants harbour carcinoma in up to 25% of cases, overexpress p53 and the DNA aneuploidy rate is increased.

Hereditary non-polyposis colorectal cancer (HNPCC, syn. hereditary mismatch repair deficiency syndrome; hMSH2 and hMLH1 are the two most frequently mutated genes): autosomal dominant with 90% penetrance, this forms 2% of colorectal cancer cases requiring three affected family members across two generations with at least one <50 years of age at presentation. Numbers of adenomas are low but they progress more quickly, forming carcinomas tending to be right-sided and multiple. Although mucinous or poorly/undifferentiated (medullary-like) in character, they are of better prognosis (66% vs. 44% 5-year survival). They have expanding or circumscribed margins, intra- and peritumoral lymphocytes, show loss of hMSH2/hMLH1 expression and are less likely to show distant spread. There is often a family history of cancer in other

*The risk of lymph node metastases being present.

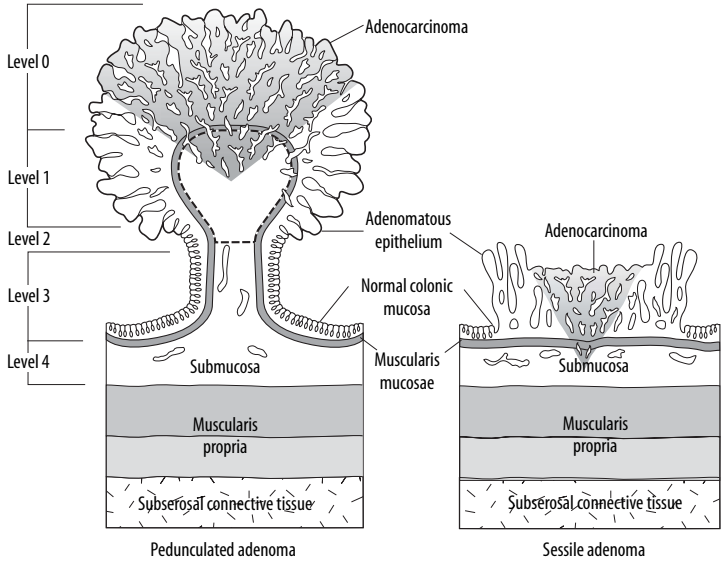


FIGURE 5.5. Malignant colorectal polyp. Levels of invasion in a pedunculated adenoma (*left*) and a sessile adenoma (*right*). The *stippled areas* represent zones of carcinoma. Note that any invasion below the muscularis mucosae in a sessile lesion represents level 4 invasion, i.e. invasion into the submucosa of the bowel wall. In contrast, invasive carcinoma in a pedunculated adenoma (*left*) must traverse a considerable distance before it reaches the submucosa of the underlying bowel wall. The *dotted line* in the head of the pedunculated adenoma represents the zone of level 1 invasion. (Haggit RC, et al. Prognostic factors in colorectal carcinomas arising in adenomas: implications for lesions removed by endoscopic polyectomy. Gastroenterology 1985;89:328–336. Copyright 1985, with permission from American Gastroenterological Association)

Therapeutic polypectomy:

— carcinoma of well or moderate differentiation
— levels of invasion 1, 2 or 3
— no lymphovascular invasion
— no involvement of the stalk resection margin

Resection indicated:

— sessile lesion with invasion (level 4)
— pedunculated lesion with level 4 invasion
— carcinoma poorly differentiated
— lymphovascular invasion
— involvement of the stalk resection margin.

viscera, e.g. stomach, small intestine, endometrium, breast, ovary, renal pelvis, and the risk of colonic cancer in a first-degree relative of an affected individual is about 50%. The tumours have a high level of microsatellite instability (MSI-H) but this applies to only a small minority (15%) of sporadic colorectal cancers, most of which show more exten-

sive chromosomal abnormalities and are microsatellite stable. Most sporadic colorectal cancers arise on the basis of the p53/APC adenome-carcinoma pathway but those with MSI-H are associated with the serrated pathway, viz, sessile serrated adenoma/mixed polyps (serrated and tubular adenoma)/sporadic MSI-H cancer. Therefore, although the vast majority of hyperplastic polyps are innocuous, large sessile serrated right-sided lesions in a young patient may be instrumental in the development of a minority of cancers.

Familial adenomatous polyposis coli: sporadic or familial and autosomal dominant with a high degree of penetrance (chromosome 5q21). The site of gene mutation can determine the phenotype and type of surgery required. A minimum of 100 colorectal polyps is required for a morphological diagnosis and these can vary from unicryptal dysplasia to macroscopic lesions. Usually thousands of polyps are present and, if left untreated, one or more cancers occur on average 20 years earlier than usual colorectal carcinomas. FAPC is also associated with adenomas and periampullary carcinoma in the duodenum (a significant cause of mortality), gastric fundic gland cyst polyps and desmoid tumours (fibromatosis).

Rates for synchronous and metachronous carcinomas range from 5 to 15%.

Associated conditions

— presentation with obstruction is adverse leading either to direct tumour perforation (pT4), proximal dilation, ischaemia and perforation (especially in the caecum) and obstructive enterocolitis. The latter can mimic inflammatory bowel disease with continuous and skip lesions of transmural inflammation either adjacent to or distant from the distal carcinoma.

Immunophenotype

— cytokeratin 20 positive/7 negative, CEA, CA19-9, sialomucin/sulphomucin, large intestinal mucus antigen (LIMA)/MUC-2, tumour associated glycoprotein (TAG-72: antibody B72.3) positive. Serum CA125 and CA19-9 may also be elevated. Sixty percent of cases are p53 positive but this does not appear to be an independent prognostic variable. Microsatellite instability–hMSH2/hMLH1 expression is preserved in the majority of sporadic microsatellite stable cancers but lost in high-level microsatellite unstable lesions, e.g. as in HNPCC. Note that some of the latter may also lose CK20 positivity and occasional cases are CK7 positive—a complicating factor in typing metastatic adenocarcinoma of unknown origin or in biopsy diagnosis of colorectal cancer with aberrant morphology. CDX-2 homeobox gene expression is positive in a majority of primary and secondary colorectal cancers. EGFR—see below.

Adjuvant therapy

— adjuvant radio-/chemotherapy induced tumour regression ± colitis. Postoperative adjuvant therapy is used for Dukes' C carcinomas and

"bad" Bs, i.e. Dukes' B carcinomas with: perforation, involved serosa, involved deep margin or extramural venous spread. These parameters score 2, 1, 1 and 1, respectively, with a total of ≥2 necessitating postoperative chemotherapy. In rectal cancer international trials are examining whether treatment should be chemotherapy or radiotherapy in isolation or combination and also pre- or postoperative. Prior to definitive surgery with curative intent, rectal cancer is assessed for evidence of local (MRI) and distant (CT) spread. Low, or clinically fixed rectal cancer with MRI evidence of significant direct or mesorectal nodal spread receives long course (6 weeks) preoperative radio-/chemotherapy instead of the more usual short course (5 days) of radiotherapy. This can induce in a significant number of cases (30–50%) marked changes of tumour regression: cell vacuolation, degeneration, apoptosis, necrosis, inflammation and fibrosis leaving only microscopic residual tumour foci. The degree of tumour response can be graded and when significant it has implications for assessing the pathological stage in the resection specimen. Its role in reducing tumour bulk at the involved deep margin is uncertain but it does seem to improve resectability. Downstaging of lymph node disease remains controversial although nodes diminish in size and number, making harvesting difficult. Response to adjuvant therapy may also depend partly on tumour genotype as to whether the cancer is positive or negative for microsatellite instability or DNA mismatch repair gene deficient or other factors such as tumour tissue levels of thymidylate synthase. Thus tumour characteristics allied to more sophisticated preoperative staging (e.g. MRI, endoluminal ultrasound combined with FNA cytology of mesorectal nodes) may allow selection of those patients who will benefit most from neoadjuvant therapy. Significantly elevated serum CEA levels correlate with either recurrent or metastatic disease. After adequate local resection of the colorectal primary, liver metastases can be excised to good effect by partial hepatectomy or subjected to targeted radiofrequency ablation. With widespread liver metastases palliative chemotherapy has a role to play—the primary may also be reduced in bulk by laser or a stent inserted across it to avoid obstruction and potential perforation with peritonitis. Novel chemotherapy in irinotecan resistant metastatic cancer is cetuximab (Erbitux), an antibody against tumour cell expression of epidermal growth factor receptor. Prior to this expensive treatment tumour EGFR positivity should be demonstrated by immunohistochemistry although, levels of tissue expression do not always correlate with tumour response.

Stage

TNM: see above.

Dukes'	A	tumour limited to the wall, nodes negative
	B	tumour beyond the muscularis propria, nodes negative
	C1	nodes positive, apical node negative
	C2	apical node positive.

Astler Coller modification:

A tumour confined to the mucosa
B1 tumour limited by muscularis propria, node negative
B2 tumour through muscularis propria, node negative
C1 tumour limited by muscularis propria, node positive
C2 tumour through muscularis propria, node positive.

Jass classification: more often used in a research setting, it assesses the extent of local tumour spread, lymph node involvement, quality of the invasive margin and density of lymphocytic infiltrate at that margin to derive a score which allocates the lesion to one of four prognostic groups, giving more refined discrimination than the usual Dukes' staging.

For routine practice Dukes' and pTNM are recommended.

Resection

RO tumour completely excised locally
R1 microscopic involvement of margin by tumour (to within 1 mm)
R2 macroscopic tumour left behind or gross involvement of margin

RO = clear proximal, distal and radial margins irrespective of serosal involvement.

Prognosis

Adverse prognosis

— tumour perforation (pT4) and obstruction.
— mucinous tumour (>50% of the tumour area).
— poor differentiation.
— splenic flexure lesion.
— male sex.
— young and old age due to delay in presentation and greater numbers of mucinous and signet ring tumours.

Prognosis relates mainly to tumour stage (particularly peritoneal and nodal spread), differentiation and adequacy of local excision with overall 5-year survival 35–40%. National screening programmes for 50–70-year-olds with 2-yearly faecal occult bloods, and if positive, follow-up colonoscopy are geared to detecting a higher percentage of Dukes' A cancers and increasing 5-year survival.

Stage	Dukes'	5-year survival	Incidence
	A	95%	15%
	B	75%	35%
	C	35%	25%
	D	25%	25%
Differentiation		Well/moderate	75%
		Poor	25%
Local excision		CRM positive	25% with 85% risk of local recurrence
		CRM negative	75% with 10% risk of local recurrence

Not infrequently there is poor correlation between surgical and histological assessment of margin clearance. A positive resection margin (usually the CRM) has strong (×12 risk) prognostic significance for local recurrence and death (×3 risk). It is one of the most important causes of morbidity in rectal cancer. Low rectal cancers also have higher recurrence rates than mid- or upper rectal tumours. For every 100 patients with colorectal cancer it is estimated that 50 will be cured, 10 will die from pelvic recurrence, five from lymphatic spread and 35 from haematogenous spread. Sites of spread are regional nodes, liver (75%), lung (15%), bone and brain (5% each). Patients with bone marrow micrometastases are reported by some to have shorter disease-free survival, but the clinical significance of the immunohistochemical and molecular detection of minimal residual disease in lymph nodes and marrow samples which are tumour negative on routine examination awaits results from large international trials.

9. OTHER MALIGNANCY

Gastrointestinal mesenchymal and stromal tumours

— Smooth muscle tumours and GISTs (rare). See also Chapters 2 and 4.

Colon

— benign appearing lesions are rare.
— usually aggressive with metastases and death related to: mitoses >6/50 hpfs, infiltrative growth pattern into the muscularis propria, mucosal invasion, cellularity, coagulative necrosis.

Anorectal

— lesions arising from the muscularis mucosae (i.e. submucosal leiomyomatous polyp) are usually treatable by local excision or polypectomy.
— lesions arising from the muscularis mucosae are considered malignant if: cellular, >5 cm diameter, infiltrative into the muscularis propria. However, if originating in the muscularis propria even bland lesions (sparse cellularity, 0–1 mitoses/50 hpfs) need long-term follow-up, as there is a tendency for local recurrence and even potential metastases.

Carcinoid tumour

— (a) chronic ulcerative colitis → enteroendocrine cell hyperplasia → microcarcinoids. (b) carcinoid polyp <1 cm diameter. (a) and (b) are benign and managed by endoscopic surveillance and biopsy. (c) ulcerated tumour: malignancy relates to: size ≥2 cm diameter, invasion beyond submucosa, angioinvasion—necessitates resection.
— lesions 1–2 cm diameter are also potentially malignant and require wide local excision.
— right colonic carcinoids tend to be large and ulcerated with adverse prognosis but the commoner rectal carcinoid is usually solitary and <1 cm in diameter. They show variable expression of neuroendocrine

markers (chromogranin negative, synaptophysin positive) and many are prostatic acid phosphatase positive which can cause diagnostic confusion with the differential diagnosis of secondary prostatic adenocarcinoma (PSA positive).

Neuroendocrine differentiation can be present in up to 50% of usual type colorectal adenocarcinomas and is not prognostically significant.

Lymphoma

— predisposing conditions are ulcerative colitis and AIDS (which can also result in Kaposi's sarcoma).
— solitary or multifocal.
— of probable mucosa-associated lymphoid tissue (MALT) origin (>70%) with a heterogeneous, polymorphous cell population: low-grade <20% blasts; high-grade >20% blasts and on a spectrum with diffuse large B-cell lymphoma.
— B (>90%) or T cell ± high content of eosinophils.
— prognosis relates to the grade and stage of disease.

Others (see Chapter 4): centrocytic or mantle cell lymphoma (multiple lymphomatous polyposis), which is of intermediate grade and aggressive. Rarely follicle centre (follicular) lymphoma spreading from systemic nodal disease; Burkitt's type/B-lymphoblastic in children or adults (with AIDS) in the terminal ileum/ileocaecal valve—high-grade lymphomas.

Leukaemia

— 50% of children with acute leukaemia who die in relapse.
— chronic lymphocytic leukaemia in the elderly and usually found incidentally in a resection done for other reasons, e.g. diverticular disease or colorectal cancer.
— granulocytic sarcoma (CD68/chloroacetate esterase/ myeloperoxidase positive).
— single/multiple deposits.

Malignant melanoma

— primary or secondary; metastases are commoner.

Kaposi's sarcoma

— AIDS/inflammatory bowel disease/HHV 8.
— 50% show visceral involvement, 8% in the hindgut.

Teratoma

— rare; primary in caecum, sigmoid and rectum but exclude spread from ovary or sacrococcygeal area. Choriocarcinoma must be distinguished from adenocarcinoma with trophoblastic differentiation.

6
Vermiform Appendix Tumours

1. GROSS DESCRIPTION

Specimen

— appendicectomy/right hemicolectomy. Usually because of acute appendicitis, an inflammatory appendix mass or as part of a colectomy for other reasons, e.g. colonic cancer. Also in the context of ovarian cystic tumours.
— length and diameter (cm).
— mucocoele/perforation/diverticulum/appendicitis/appendicular mass.

Tumour

Site
— tip/base/diverticulum/body.

Size
— length × width × depth (cm) or maximum dimension (cm).

Appearance
— polypoid/sessile/plaque/ulcerated/infiltrative/mucoid/yellow.

Edge
— circumscribed/irregular.

2. HISTOLOGICAL TYPE

Carcinoid (endocrine cell) tumours
— 0.5–1.5% of appendicectomies.
— 85% of appendiceal tumours.
— usually a coincidental finding of yellow pale tumour at the tip, although it may contribute to appendicitis when at the appendix base (10%).
— variably chromogranin, synaptophysin, CD56 positive depending on EC (usual) or L cell origin.

Usual type: 70% of cases and at the appendiceal tip. Solid nests/cords/ribbons/acini of uniform cells often with invasion of muscularis,

± serosa and lymphatics. Benign with appendicectomy the treatment of choice.

Rarely cases spread to peritoneum, regional nodes and liver (35% 5-year survival) and these are usually >2 cm diameter with size the main factor predictive of behaviour. Radical surgery should be considered in these circumstances. Extensive invasion of mesoappendix and the appendiceal base are also adverse indicators.

Goblet cell carcinoid (mucinous/adenocarcinoid/crypt cell carcinoma) type: clusters, strands or glandular collections of mucus-secreting epithelial cells often with a signet ring or goblet cell morphology. Usually only a minor population of endocrine cells is present demonstrated by immunohistochemistry. Potential for extra-appendiceal spread (20% of cases) and occasionally involvement of regional nodes and liver. Propensity for transcoelomic spread to involve ovaries and direct spread through the appendix base and into the caecum.

Right hemicolectomy should be considered, particularly if there is extensive spread with an infiltrative growth pattern, involvement of the appendix base or tumour pleomorphism and mitoses. The term mixed carcinoid/adenocarcinoma is sometimes used if there is an infiltrating component of colorectal type tumour tissue and again radical surgery should be considered.

Distinguish from: (1) secondary colorectal carcinoma involving the appendix either directly (e.g. from caecal pouch) or via the peritoneum (signet ring cell carcinoma of rectosigmoid area), and (2) primary colonic-type mucinous adenocarcinoma of appendix, which is aggressive in behaviour and requires radical surgery. A pre-existing mucosal adenoma in a carcinoma and the component of endocrine cells in a carcinoid lesion may help in this respect.

Adenoma

— <1% of appendicectomies and the majority are benign.
— localized (polypoid—rare) or diffuse.
— tubular/tubulovillous/villous* with variable grades of dysplasia.
— *see Mucocoele (Appendiceal Mucinous Neoplasms).
— the adenomatous mucosa can be flattened and simplified, or serrated.
— in up to 20–40% of cases there are adenomas or adenocarcinomas elsewhere in the colorectum.

Adenocarcinoma

— 0.1% of appendicectomies.
— requires destructive invasion through the muscularis mucosae by malignant glands (sometimes but often not with a desmoplastic reaction), or the presence of epithelium in extra-appendiceal mucus (cytokeratins and CEA can be useful in demonstrating this). The latter can be difficult to distinguish from a LAMN with mucin dissection and peritoneal spillage (see below).
— identified as primary by a mucosal adenomatous lesion.

— histologically of usual colorectal type, often well differentiated mucinous in character.
— rarely signet ring cell carcinoma: distinguish from goblet cell carcinoid (chromogranin positive) and metastatic gastric/breast carcinoma (infiltrating lobular type). In this respect it is necessary to know of previous operations to the stomach and breast and these sites may have to be investigated. Breast carcinoma may also be ER/PR positive and cytokeratin 7 positive/20 negative, whereas gut cancers are usually CEA positive and cytokeratin 20 positive/7 negative. The intracytoplasmic vacuoles of lobular carcinoma are PAS-AB positive.
— treatment is right hemicolectomy and regional lymphadenectomy. Prognosis reflects the histological grade of tumour and Dukes' classification, with an overall 5-year survival rate of 60–65% with hemicolectomy but only 20% for appendicectomy alone.

Metastatic carcinoma
— peritoneal spread: colorectum, ovary, stomach.
— distant spread: lung, breast.

3. DIFFERENTIATION

Well/moderate/poor/undifferentiated, or, Grade 1/2/3/4 based on the percentage tumour gland formation (well/G1 > 95%; moderate/G2 50–90%: poor/G3 < 50%) for adenocarcinoma.

Undifferentiated carcinoma (grade 4) shows no gland formation.

Epithelial/enteroendocrine/mixed (the behaviour and prognosis is determined by that of the individual components).

4. EXTENT OF LOCAL TUMOUR SPREAD

Border: pushing/infiltrative.

Lymphocytic reaction: prominent/sparse.

Limited to the appendix, into mesoappendix, appendiceal base and caecum.

As in colorectal carcinoma, prognosis relates to Dukes' stage:

A tumour confined to the appendix wall, nodes negative
B tumour through the appendix wall, nodes negative
C tumour in regional lymph nodes irrespective of the depth of wall invasion.

In the 6th edition TNM classification appendix is an anatomical subsite of colorectum and it applies only to carcinoma.

pTis carcinoma in situ: intraepithelial (within basement membrane) or invasion of the lamina propria (intramucosal) with no extension through muscularis mucosae into submucosa
pT1 tumour invades submucosa
pT2 tumour invades muscularis propria
pT3 tumour invades beyond muscularis propria into subserosa or mesoappendix

pT4 tumour invades the serosal surface or adjacent organs and/or perforation of visceral peritoneum.

5. LYMPHOVASCULAR INVASION

Present/absent.

Intra-/extratumoral.

Serosa/mesoappendix.

Lymphovascular invasion in adenocarcinoma is more significant than in a usual carcinoid tumour, where it is quite common with no adverse prognostic effect.

6. LYMPH NODES

Site/number/size/number involved/limit node/extracapsular spread.

Regional nodes: ileocolic. A regional lymphadenectomy will ordinarily include a minimum of 12 lymph nodes.

Dukes' C: metastasis in regional lymph nodes.

pN0 no regional lymph node metastasis
pN1 1–3 involved regional lymph nodes
pN2 4 or more involved regional lymph nodes.

7. EXCISION MARGINS

Distance (mm) to the proximal limit of excision.

8. OTHER PATHOLOGY

Carcinoid syndrome rarely occurs due to the scarcity of appendiceal carcinoid tumours metastatic to the liver.

Mucocoele

Mucocoeles of obstructed or non-obstructed types both result in marked distension of the lumen by abundant mucus. Obstructed mucocoele is usually <1–2 cm diameter and effectively a retention cyst lined by variably attenuated, atrophic mucosa. The commoner non-obstructed mucocoeles are generally >1–2 cm diameter and due to an abnormality of the underlying mucosa caused either by hyperplastic change (diffuse or polyp), mucinous cystadenoma or mucinous adenocarcinoma. The latter two lesions comprise the group of appendiceal mucinous neoplasms which can be either low-grade (LAMN: mucinous cystadenoma) or high-grade (MACA: mucinous adenocarcinoma) and are of particular relevance to formation of pseudomyxoma peritonei and ovarian mucinous cystic tumours. LAMNs often have a bland attenuated epithelial lining, which can be confined to the mucosa or dissect through the appendiceal wall.

Pseudomyxoma peritonei

Mucocoeles can be associated with perforation or mucin dissection resulting in pseudomyxoma peritonei which is either localized or diffuse. Obstructed mucocoeles and those due to hyperplastic change and

mucosa-confined adenoma usually remain localized, whereas diffuse pseudomyxoma is due to spillage of either atypical or unequivocally malignant epithelium associated with a LAMN or appendiceal adenocarcinoma, respectively. Prognosis relates to the extent of extra-appendiceal mucus and the cellularity and atypia of the neoplastic cells within it. However, generalized abdominopelvic disease can result even when the epithelial component is cytologically bland and relatively scanty. Diffuse pseudomyxoma may be helped by debulking procedures but is largely refractory to treatment, slowly but relentlessly progressive and causes death by bowel obstruction (45% 10-year survival). In this condition there is also a strong association with intestinal-type mucinous tumours of the ovary of borderline malignancy which are now regarded as being an implantation deposit from the appendix. Comparative immunophenotyping can help determine the relationship between the tumours. In this respect it should be noted that up to 5% of appendiceal mucinous adenocarcinomas express CK7 as well as the usual CK20. Ovarian mucinous tumours are also CK7/CK20 positive, indicating either an ovarian primary or possible spread from appendix. If CK20 positive alone it is most likely a deposit from an appendiceal or other colorectal lesion. Ovarian tumours of mucinous type can show a wide spectrum of intestinal differentiation and it may be that a significant number of these represent deposits from appendiceal, colonic, gastric or pancreatic sites. In addition, the appendiceal lesion may not be grossly evident and it is recommended that appendicectomy be carried out, particularly if the ovarian tumours are bilateral and mucinous peritoneal disease is present. Occasionally pseudomyxoma peritonei may be due to mucinous carcinomas from other sites, e.g. stomach, colorectal, gall bladder, breast or lung.

Synchronous/metachronous colorectal lesions.

The presence of hyperplastic, adenomatous or cystadenocarcinomatous epithelium in the appendix is a marker of concurrent or subsequent epithelial neoplasms elsewhere in the colorectum.

Appendicitis can form an inflammatory appendix mass in the right iliac fossa that mimics colorectal cancer clinically and radiologically. Appendiceal tumours may also present in this fashion.

9. OTHER MALIGNANCY

Malignant lymphoma

— primary (rare) or secondary to systemic/nodal disease.
— Burkitt's lymphoma: ileocaecal angle in childhood and aggressive high-grade disease.

Kaposi's sarcoma

— AIDS.

7

Anal Canal Carcinoma (with comments on pelvic exenteration)

1. GROSS DESCRIPTION

Specimen

— anal tumours present as a mass or feeling of fullness. For therapeutic reasons clear clinicopathological distinctions must be made
  - rectal type adenocarcinoma arising from the distal rectum or the colorectal zone of the upper anal canal can spread downwards and present as an anal tumour. Treatment is surgical (APR) ± neoadjuvant therapy (see Chapter 5).
  - anal canal squamous carcinoma can spread upwards or downwards presenting as low rectal or perianal/anal margin tumour, respectively. Treatment is primarily radio-/chemotherapy and not surgical.
  - perianal/anal margin squamous carcinoma can be confined to the skin or spread to involve the distal anus. Treatment is local surgical excision for the former and more radical surgery or radiotherapy alone or in combination for the latter.
  - anal canal adenocarcinoma, malignant melanoma or sarcoma are surgically resected.
  - investigation of anal tumours is by anoproctoscopy and biopsy with endoanal ultrasound, MRI and CT scans to stage biopsy-proven disease.
— biopsy/resection (local or abdominoperineal).
— weight (g) and size/length (cm), number of fragments.

Tumour

Site

— mucous membrane/muscularis/extramural.
— low rectal/anal canal/perianal margin or skin.
— anatomy:
  1. upper zone: colorectal mucosa
  2. transitional/cloacal zone: stratified cuboidal epithelium with surface umbrella cells + anal glands in submucosa
     _____ dentate (pectinate) line _____
  3. lower zone: stratified squamous epithelium continuous with appendage bearing perianal skin.

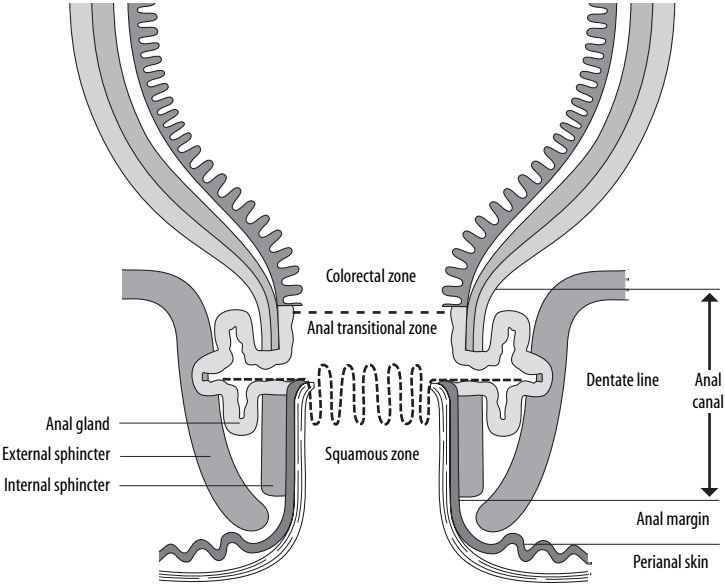


FIGURE 7.1. The anatomy of the anal canal. (Williams GR, Talbot IC. Anal carcinoma: a histological review. Histopathology 1994;25:507–516 Reproduced with permission from Blackwell Publishing Ltd)

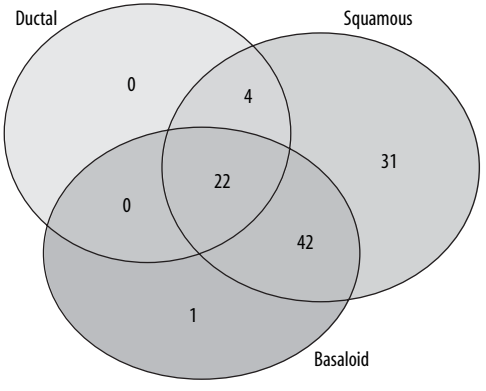


FIGURE 7.2. Anal canal carcinoma: overlap in histological subtypes. (Williams GR, Talbot IC. Anal carcinoma: a histological review. Histopathology 1994;25:507–516 Reproduced with permission from Blackwell Publishing Ltd)

Size
— length × width × depth (cm) or maximum dimension (cm).

Appearance
— polypoid/sessile/ulcerated/stricture/pigmented/ fleshy/mucoid.

Edge
— circumscribed/irregular.

2. HISTOLOGICAL TYPE

Anal margin/perianal skin
As for non-melanocytic skin carcinoma (Chapter 20), in particular well-differentiated keratinizing squamous cell carcinoma and variants including verrucous carcinoma. Also basal cell carcinoma, Bowen's disease, Paget's disease.

Anal canal
Carcinoma of the anal canal is regarded as being a squamous cell carcinoma showing variable degrees of squamous (in >90% of cases), basaloid (in 65% of cases) and ductular (in 26% of cases) differentiation. Distal canal and anal margin cancers tend to show more overt squamous differentiation (well differentiated).

Squamous cell carcinoma
— keratinizing/non-keratinizing large cell.

Basaloid carcinoma
— (syn. cloacogenic/non-keratinizing small cell squamous carcinoma).
— palisading nests of basophilic cells with surrounding retraction artefact, central eosinophilic necrosis ± ductular differentiation.
— comprises 50% of anal carcinomas.
— mixed basaloid/squamous types.
— increased incidence in Crohn's disease, smoking, immunosuppression and sexually transmitted disease.
— association with HPV 16/18 and anal intraepithelial neoplasia (AIN).

Others
Mucinous (colloid) adenocarcinoma: in anal fistula which may be associated with Crohn's disease or hindgut duplication.

Anal gland adenocarcinoma: rare. In contrast to anorectal adenocarcinoma lacks O-acetylsialomucin (PAS negative post PB-KOH saponification). Late diagnosis, poor prognosis.

Extra-mammary Paget's disease: in 20% an underlying adnexal or rectal adenocarcinoma is found. The majority remain confined to the surface epithelium.

Neuroendocrine carcinoma: carcinoid/small cell/large cell; carcinoid <2 cm is treated by local excision, if ≥2 cm consider more radical surgery.

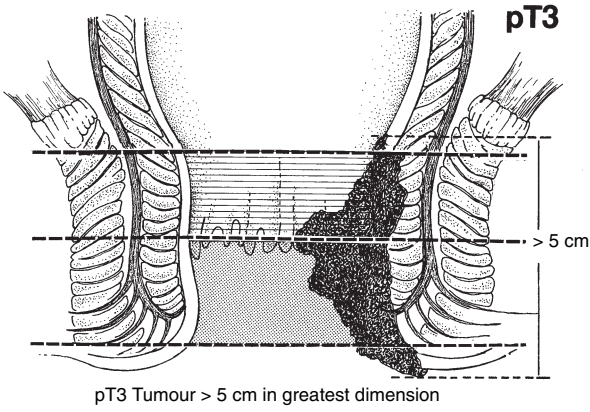


FIGURE 7.3. Anal canal carcimoma.

Spindle cell carcinoma: rare.

Squamous cell carcinoma with microcysts: worse prognosis.

Malignant melanoma: primary mucosal origin with adjacent junctional atypia that can be destroyed by surface ulceration. 1.5% of anal malignancy—aggressive with early spread and death in months (liver, lung metastases). Spindle cell or epithelioid.

Metastatic carcinoma: direct spread—adenocarcinoma of rectal type arising from the colorectal mucosa of the upper anal zone cannot be distinguished from usual low rectal carcinoma and is grouped with it. Prostatic carcinoma (PSA/PSAP positive) and cervical carcinoma.

3. DIFFERENTIATION

Well/moderate/poor/undifferentiated or Grade 1/2/3/4.

For squamous cancers differentiation features are keratinization and intercellular bridges, and for adenocarcinomas the percentage tumour gland formation (well/G1 >95%; moderate/G2 50–95%; poor/G3 <50%). Undifferentiated carcinomas (no gland formation) are classified as grade 4.

Sarcoma: low-grade/high-grade based on necrosis, atypia and mitotic counts.

4. EXTENT OF LOCAL TUMOUR SPREAD

Border: pushing/infiltrative.

Lymphocytic reaction: prominent/sparse.

Depth of spread: submucosa; muscularis of rectum or anal sphincters; extrarectal and extra-anal tissue including ischiorectal fossae and pelvic structures. Clinical assessment is by MRI and endoanal ultrasound for local spread, and CT scan for distant disease.

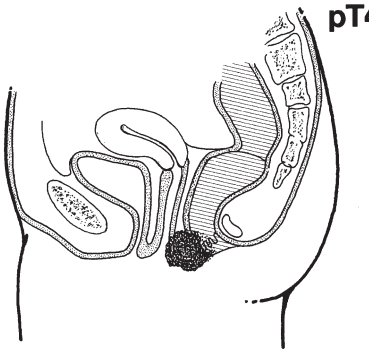


FIGURE 7.4. Anal canal carcinoma.

At diagnosis the majority have spread through sphincteric muscle into adjacent soft tissue.

The TMN classification applies only to carcinomas.

pTis carcinoma in situ
pT1 tumour ≤ 2 cm in greatest dimension
pT2 2 cm < tumour ≤ 5 cm in greatest dimension
pT3 tumour > 5 cm in greatest dimension
pT4 tumour of any size invading adjacent organ(s), e.g. vagina, urethra, bladder.

5. LYMPHOVASCULAR INVASION

Present/absent.
Intra-/extratumoral.
Perineural spread.

Distant metastases at the time of diagnosis are present in 5–10% of cases. Haematogenous spread is to liver, lung and skin.

6. LYMPH NODES

Site/number/size/number involved/limit node/extracapsular spread.
Regional nodes: perirectal, internal iliac, inguinal. Anal margin tumours go initially to inguinal nodes → iliac nodes. Anal canal tumours go initially to haemorrhoidal nodes → perirectal and inguinal nodes. A regional lymphadenectomy will ordinarily include a minimum of 12 lymph nodes.

pN0 no regional lymph node metastasis
pN1 metastasis in perirectal lymph node(s)
pN2 metastasis in unilateral internal iliac and/or inguinal lymph node(s)
pN3 metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes.

Lymph node involvement is present in 10–50% of cases at presentation.

7. EXCISION MARGINS

Distances (mm) to the nearest longitudinal (rectal or perianal) resection limit and deep circumferential radial margin.

8. OTHER PATHOLOGY

Carcinoma of the anal canal (F:M 3:2) is commoner (3:1) than carcinoma of the anal margin (M:F 4:1).

Human papilloma virus infection is a common aetiological agent associated with a spectrum of anal viral lesions, preneoplasia (AIN) and carcinoma. HPV subtypes 16 and 18 are particularly neoplasia progressive. Infection with HIV and other sexually transmitted viruses also contributes.

Condyloma accuminatum, giant condyloma of Buschke-Löwenstein, and Bowen's disease of anal skin are associated with perianal margin/skin squamous carcinoma and its variants. Some authors equate giant condyloma to verrucous carcinoma (indolent growth, exophytic, deep bulbous processes with bland cytology, more aggressive after radiotherapy). Bowenoid papulosis (perineal brown patches, histology of Bowen's disease) has no significant malignant potential.

Concurrent cervical intraepithelial neoplasia (CIN) and AIN grades I, II, III are associated with anal canal carcinoma, with AIN being present in up to 55% of cases. A premalignant phase or model of progression in AIN is not as well established as in CIN, although cancer risk appears to be greatest for high-grade (III) AIN.

The majority of anal canal carcinomas arise in the vicinity of the dentate line from the transitional/cloacal zone and spread preferentially upwards in the submucosal plane, thereby presenting as ulcerating tumour of the lower rectum. Due to the differential options of primary adjuvant therapy vs. primary resection, anal canal carcinoma must be distinguished by biopsy from both rectal adenocarcinoma superiorly and basal cell carcinoma or squamous cell carcinoma of the perianal margin/skin inferiorly.

Anal Paget's disease must be distinguished from Bowen's disease and pagetoid spread of malignant melanoma. Mucin stains and immunohistochemistry are necessary (mucicarmine, PAS ± diastase, cytokeratins, melanoma markers: pigment, S100, HMB-45, melan-A). It may be associated with concurrent or subsequent anal, or, low rectal adenocarcinoma with the Paget's cells showing intestinal-type gland formation and cytokeratin 20 positivity. More often it is a primary anal epithelial lesion lacking intestinal glandular differentiation and cytokeratin 20 positivity but cytokeratin 7/GCDFP-15 positive and which may progress to submucosal invasion. A majority remain as intraepithelial malignancy. A further differential diagnosis is pagetoid spread from a primary anorectal signet ring cell carcinoma. Immunohistochemistry is also important in the differential diagnosis of anal basaloid carcinoma (cytokeratins, EMA, CEA positive), malignant melanoma, lymphoma (CD45 positive), spindle cell carcinoma (cytokeratin positive) and leiomyosarcoma (desmin, h-caldesmon, smooth muscle actin positive). Distinction

between anal canal basaloid carcinoma and basal cell carcinoma of the anal margin is by the anatomical location as well as histological characteristics.

Radiotherapy necrosis.

Leukoplakia with or without AIN is occasionally seen and needs biopsy to establish the presence of dysplasia.

Prognosis

Carcinoma of anal margin/perianal skin is treated primarily by surgery ± radiotherapy. Anal canal squamous carcinoma responds well to primary radio-/chemotherapy and abdominoperineal resection is reserved for extensive/recurrent/non-responsive tumours or other lesions such as malignant melanoma and leiomyosarcoma. Perianal carcinoma: 5-year survival 85%; anal canal carcinoma: 5-year survival 65–80%. Adverse prognostic indicators are advanced stage or depth of spread, tumour in inguinal nodes (10–50%) and post-treatment recurrence in the pelvic and perianal regions, e.g. pT1 carcinoma has a 5-year survival of 91%, pT3 16%. Histological grade is not a strong indicator but may be helpful in poorly differentiated squamous cell carcinoma of large cell type. Ductal differentiation in basaloid carcinoma is an adverse factor. Recurrence in men is pelvic and perineal, in women pelvic and vaginal.

9. OTHER MALIGNANCY

Lymphoma/leukaemia

— secondary to systemic/nodal disease.
— AIDS.

Leiomyosarcoma

— low-grade/high-grade based on cellularity, atypia, necrosis, infiltrative margins and mitoses. Desmin, h-caldesmon positive.

Presacral tumours

— teratoma, peripheral neuroectodermal tumours (including Ewing's sarcoma), myeloma, metastatic carcinoma.

Rhabdomyosarcoma

— childhood, embryonal (desmin/myo D1/myogenin positive).

10. COMMENTS ON PELVIC EXENTERATION

In general pelvic exenteration is considered for locally advanced or recurrent pelvic malignancy in the absence of extra-pelvic metastases.

— degree of disease spread is assessed by
  - CT scan—pelvic and retroperitoneal lymphadenopathy, extra-pelvic metastases.
  - MRI scan—local cancer spread.
  - PET/CT scan—detects metabolic activity in malignant tumours and is useful in localizing recurrent or metastatic disease.

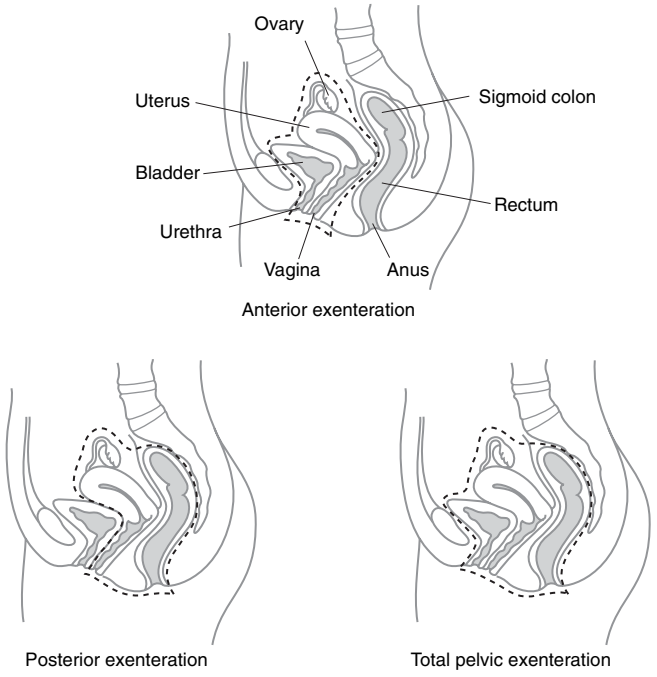


FIGURE 7.5. Pelvic exenterations.

— relevant malignancies are: cervical carcinoma, rectal carcinoma, anal carcinoma, soft tissue lesions [e.g. malignant fibrous histiocytoma (MFH), aggressive angiomyxoma], aggressive muscle invasive bladder cancer, and occasionally advanced endometrial, vaginal or vulval cancers.
— contraindications are significant comorbidity, distant metastases (except resectable liver metastases from a rectal carcinoma) and involvement of major pelvic vessels, nerves, side walls or sacrum (but can be resected en bloc in rectal cancer).
— preoperative adjuvant therapy may result in significant tumour regression, so much so that it may be difficult to find residual disease and lymph nodes which hyalinize. Deep spread and margins fibrose, making accurate assessment of pT stage and resection status problematic.
— surgery may be with curative intent or palliative to obviate complex and debilitating pelvic symptoms due either to spread of malignancy or as a consequence of adjuvant therapy, e.g. pain, fistulae.

— pelvic exenterations
  - anterior: bladder, lower ureters, reproductive organs, draining lymph nodes and pelvic peritoneum.
  - posterior: rectum, distal colon, internal reproductive organs, draining lymph nodes and pelvic peritoneum.
  - total: anterior and posterior.
— principles of specimen reporting
  - identify the specimen type and component organs.
  - block limits, i.e. ureters, urethra, vagina and proximal/distal bowel.
  - paint circumferential radial fascial margins, comment on the uterine/bladder dome/colonic/upper anterior rectal peritoneum and integrity of the mesorectum and its fascia.
  - sagittal hemisection can be very useful in demonstrating the relationships between the tumour and the constituent organs. Fistulae can be cut along the line of an exploring probe. Also document the status of circumferential radial margins.
  - report as per individual cancers, noting in particular the degree of locoregional spread, margin status and effect of preoperative adjuvant therapy.

8
Gall Bladder Carcinoma

1. GROSS DESCRIPTION

Specimen

— gall bladder disease presents generally in middle-aged to elderly females with dyspepsia, bloating and right hypochondrial pain. Investigation includes liver function tests and abdominal ultrasound scan looking for luminal/mural lesions, calculi or large duct obstruction. If abnormal, CT scan and cholangiography [percutaneous or at endoscopic retrograde cholangiopancreatography (ERCP)] are of use in demonstrating and staging a tumour mass.
— laparoscopic/open cholecystectomy. Most gall bladder cancers are an incidental finding after routine cholecystectomy. Rarely, they are submitted as part of an elective extended cholecystectomy—after determination of the extent of local spread by operative ultrasound the hepatic gall bladder bed and regional nodes are resected. A deeper tumour may require hepatic segmental resection.
— size (cm) and weight (g).
— open/intact.
— contents: bile/calculi (number, size, shape, colour).
— lymph nodes: site/size/number.

Tumour

Site

— fundus (50%)/body/cystic duct.

Size

— length × width × depth (cm) or maximum dimension (cm).

Appearance

— grossly apparent/inapparent.
— diffuse (65%)/polypoid (30%—including papillary)/ulcerated.

Edge

— circumscribed/irregular.

2. HISTOLOGICAL TYPE

More than 90 % of gall bladder cancers are adenocarcinoma.

Adenocarcinoma

— tubular/acinar: usual type and a well to moderately differentiated biliary pattern of low cuboidal to tall columnar cells.
— papillary: polypoid/well differentiated/better prognosis.
— intestinal/mucinous/signet ring cell/clear cell: unusual. Distinguish from metastatic stomach or bowel cancer by adjacent mucosal dysplasia. Mucinous/signet ring cell carcinomas require >50% of the tumour to be composed of this pattern.

Adenosquamous carcinoma

Squamous carcinoma

Small cell carcinoma

— and other neuroendocrine lesions, e.g. carcinoid/large cell neuroendocrine carcinoma including composite tumours (carcinoid/adenocarcinoma).
— small cell carcinoma is aggressive and may be a component of usual adenocarcinoma.

Spindle cell carcinoma/carcinosarcoma

— biphasic carcinoma/sarcoma-like components ± specific mesenchymal differentiation. These represent carcinomas with variable stromal differentiation and overlap with undifferentiated carcinoma.
— elderly patients, poor prognosis.

Undifferentiated carcinoma

— nodular and solid/spindle cell/giant cell/osteoclast-like giant cell variants.

Malignant melanoma

— secondary (15% of disseminated melanoma at autopsy) or rarely primary (nodular, adjacent mucosal junctional change).

Metastatic carcinoma

— direct spread: stomach, colon, pancreas, cholangiocarcinoma.
— distant spread: breast, lung, kidney.

Note that cystic duct carcinoma is classified as a tumour of the extrahepatic bile ducts.

3. DIFFERENTIATION

Well/moderate/poor/undifferentiated, or Grade 1/2/3/4 based on the percentage tumour gland formation (well/G1 >95%; moderate/G2 50–95%; poor/G3 <95%).

— usually well to moderately differentiated arising from a sequence of mucosal intestinal metaplasia and dysplasia.
— signet ring cell carcinoma is grade 3, small cell and undifferentiated carcinoma (no gland formation) grade 4.

4. EXTENT OF LOCAL TUMOUR SPREAD

Border: pushing/infiltrative.
Lymphocytic reaction: prominent/sparse.
Characteristic perineural spread (25% of cases).

The TNM classification applies only to carcinomas.

pTis carcinoma in situ
pT1 tumour limited to gall bladder wall
a. lamina propria
b. muscularis
pT2 tumour invades perimuscular connective tissue, no extension beyond serosa or into liver
pT3 tumour perforates serosa and/or directly invades the liver and/or directly invades one adjacent organ, e.g. stomach, duodenum, colon, pancreas, omentum, extrahepatic bile ducts
pT4 tumour invades main portal vein or hepatic artery, or invades two or more extrahepatic organs or structures.

Note that carcinoma in situ and adenocarcinoma may extend into Rokitansky-Aschoff sinuses and this must be distinguished from deeply invasive tumour which shows a lack of low-power lobular organization, deficient basement membrane and stromal desmoplasia.

5. LYMPHOVASCULAR INVASION

Present/absent.
Intra-/extratumoral.
Perineural invasion is an adverse prognostic factor.

6. LYMPH NODES

Site/number/size/number involved/limit node/extracapsular spread.
Regional nodes: cystic duct node, pericholedochal, hilar, peripancreatic, periduodenal, periportal, coeliac and superior mesenteric. A regional lymphadenectomy will ordinarily include a minimum of three lymph nodes.

pN0 no regional lymph node metastasis
pN1 metastasis in regional lymph node(s).

The most commonly involved lymph nodes are the pericholedochal.

7. EXCISION MARGINS

Distances (mm) of tumour to the proximal limit of the cystic duct.

Mucosal dysplasia in adjacent gall bladder mucosa, the cystic duct and its limit. Histological detection of mucosal dysplasia in a routine

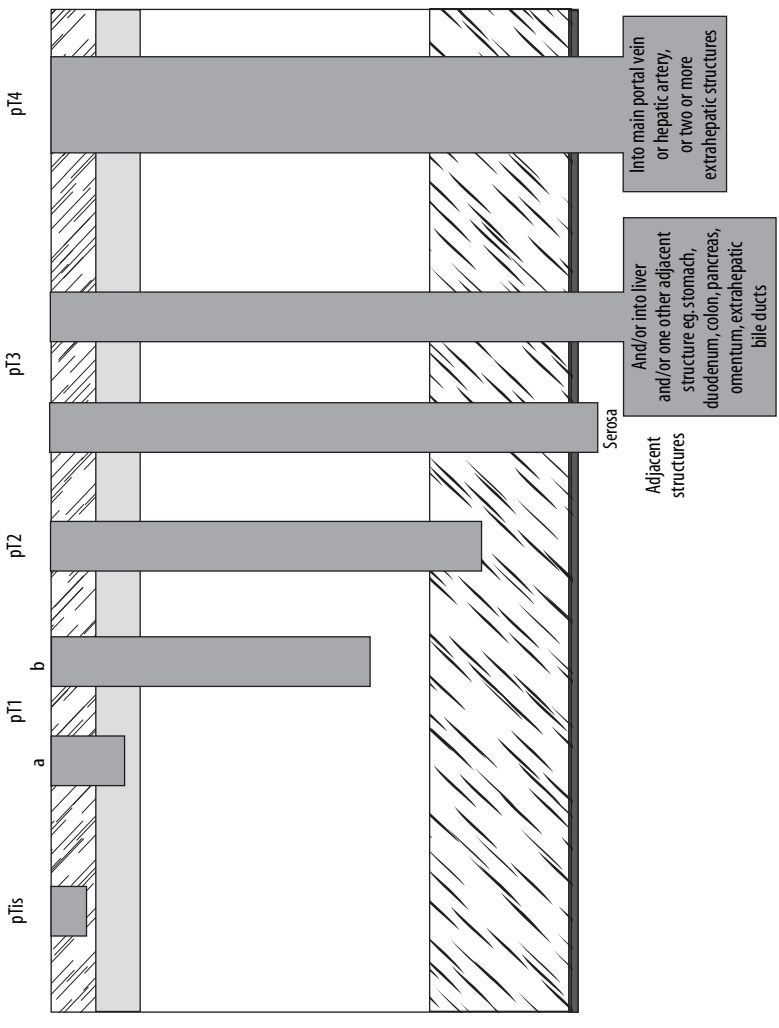


Figure 8.1. Gall bladder carcinoma.

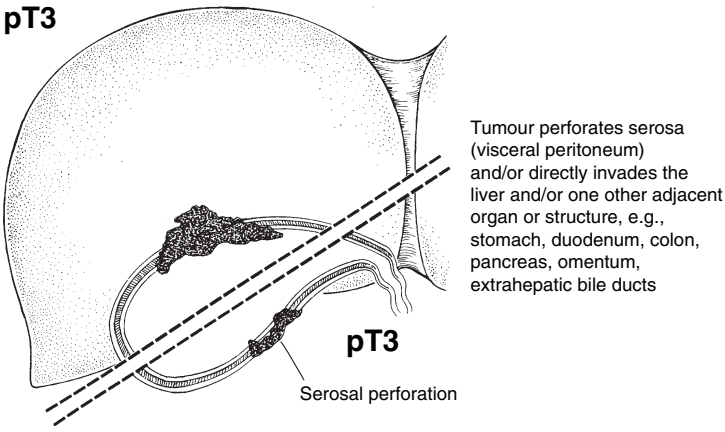


FIGURE 8.2. Gall bladder carcinoma.

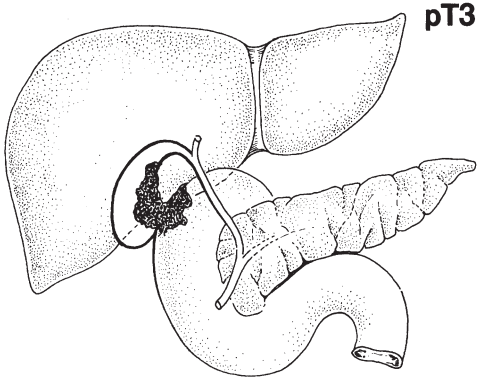


FIGURE 8.3. Gall bladder carcinoma.

cholecystectomy block should prompt extra blocks to look for an occult invasive cancer

8. OTHER PATHOLOGY

Adenoma—rare (0.5% cholecystectomies)—exclude FAPC. As in colorectum, the risk of malignancy increases with size, villousity and degree of dysplasia. There are intestinal, pyloric gland and biliary histological subtypes. A true adenoma should not be confused with the commoner fundal cholecystitis glandularis proliferans—a reactive mucosal hyperplasia associated with smooth muscle proliferation.

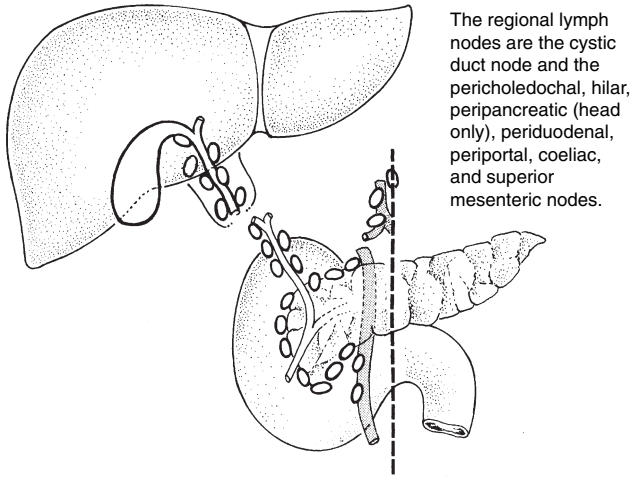


FIGURE 8.4. Gall bladder: regional lymph nodes.

Immunophenotype
Gall bladder carcinoma is cytokeratin (CAM5.2, AE1/AE3, CK7, CK19-9), CA19-9 and CEA positive.

Prognosis
Calculi, and anomalous choledochopancreatic duct anatomy are risk factors, with calculi present in 80–90% of cases in female patients (F:M 3:1) particularly responsible. Most gall bladder carcinomas are clinically inapparent and found incidentally as diffuse thickening of the wall at cholecystectomy for gall stones. Prognosis is better if lesions are of papillary type, low histological grade and confined to the mucous membrane, when resection is potentially curative (90% 5-year survival). A significant number of carcinomas are grossly inapparent and a microscopic finding only. However, curative resection is unusual and up to 50% present with regional node metastases and involvement of the gall bladder bed liver. In these patients 5-year survival rates are 5–10%.

9. OTHER MALIGNANCY

Lymphoma/leukaemia
— MALToma or more usually secondary to systemic nodal disease.

Sarcoma (rare)
— embryonal rhabdomyosarcoma (children: desmin/myo D1/myogenin positive), leiomyosarcoma, angiosarcoma.

9
Extrahepatic Bile Duct Carcinoma

1. GROSS DESCRIPTION

Specimen

— extrahepatic bile duct cancer presents with obstructive jaundice and investigation includes serum CA19-9 levels, liver function tests, ultrasound scan and cholangiography (either MR, percutaneous or at ERCP) to detect large duct obstruction and strictures, and CT/MRI scan for tumour staging.
— cytological brushings and washings/biopsy/resection.

Cytology material is obtained at ERCP, which is used either for diagnostic or therapeutic purposes (stone retrieval, stent insertion). Diagnostic yields for malignancy are at best 30–40% and a presumptive working diagnosis may have to be based on clinical grounds. Radical resection is usually for a distal bile duct or ampullary mass (Whipple's pancreaticoduodenectomy) causing obstructive jaundice, which may or may not have been proven by ERCP brushings or endoscopic biopsy of the ampulla or duodenal papilla. Sometimes a segmental resection for a mid bile duct tumour is carried out, or occasionally combined with hepatic segmental resection for a proximal or infrahilar tumour.

— weight (g) and size/length (cm), number of fragments.

Tumour

Site

— tumours of the extrahepatic ducts are outside the liver and above the level of the ampulla of Vater. Cystic duct and choledochal cyst tumours are included.
— hilum/proximal third (50–60%: equally between the right/left/common hepatic, cystic and upper common bile ducts), intermediate third (25%), distal third (10%), multifocal/diffuse (15%).

Size

— length × width × depth (cm) or maximum dimension (cm).
— localized (a majority), the entire common bile duct or multifocal throughout the extrahepatic biliary system.

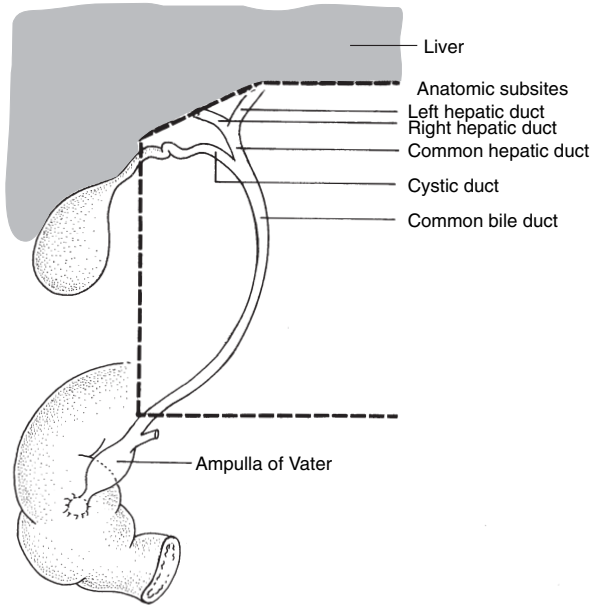


FIGURE 9.1. Extrahepatic bile ducts.

Appearance
— papillary/polypoid: distal third.
— nodular: intermediate third.
— ulcerated/sclerotic/scirrhous: proximal third.

The majority are nodular or sclerosing with deep penetration of the wall, a small minority have a cystic component.

Edge
— circumscribed/irregular.

2. HISTOLOGICAL TYPE

Adenocarcinoma
— tubular/acinar: usual type and a well to moderately differentiated biliary pattern of low cuboidal to tall columnar cells.
— papillary: polypoid and well differentiated in the distal third with a better prognosis.
— intestinal: well to moderate differentiation ± mucin secretion in a fibrous stroma.
— sclerosing: hilar (Klatskin) tumour. Well to moderately differentiated tubular adenocarcinoma and rarely mucinous or signet ring cell. Fibrous nodule, short or long segmental stenosis, or papillary.

Indolent growth with potentially prolonged survival. Arises in a field of dysplasia and resection limits should be checked for this.
— mucinous carcinoma/signet ring cell carcinoma (>50% of the tumour area), clear cell carcinoma are unusual.
— cystadenocarcinoma: a small number are the malignant counterpart of bile duct cystadenoma with variable benign, borderline and focal malignant change. Middle-aged females, resectable, good prognosis.

Adenosquamous carcinoma

Squamous cell carcinoma

Small cell carcinoma
— and other neuroendocrine lesions, e.g. carcinoid tumour.

Carcinosarcoma/spindle cell carcinoma
— cytokeratin positive spindle cells and varying degrees of stromal mesenchymal differentiation.

Undifferentiated carcinoma
— nodular or solid/spindle cell/giant cell variants.

Malignant melanoma
— metastatic or primary (rare).

Metastatic carcinoma
— colorectum, breast (infiltrating lobular), kidney.

3. DIFFERENTIATION

Well/moderate/poor/undifferentiated, or Grade 1/2/3/4 based on the percentage tumour gland formation (well/G1 >95%; moderate/G2 50–95%; poor/G3 <50%).

Signet ring cell carcinoma is grade 3, small cell and undifferentiated carcinoma (no gland formation) grade 4—these are prognostically adverse cancers.

4. EXTENT OF LOCAL TUMOUR SPREAD

Border: pushing/infiltrative.
Lymphocytic reaction: prominent/sparse.

Perineural spread is a characteristic and may be present beyond the resection line causing surgical failure.

The TNM classification applies to carcinomas of the extrahepatic bile ducts and those of choledochal cysts.

pTis carcinoma in situ
pT1 tumour confined to the bile duct* histologically

*The wall of the bile duct comprises the subepithelial connective tissues and underlying fibromuscular layer.

pT2 tumour invades beyond the wall of the bile duct*
pT3 tumour invades adjacent structures: liver, pancreas, gall bladder and/or unilateral tributaries of the portal vein or hepatic artery
pT4 tumour invades any of the following: main portal vein or its tributaries bilaterally, common hepatic artery, or other adjacent structures, e.g. colon, stomach, duodenum, abdominal wall.

5. LYMPHOVASCULAR INVASION

Present/absent.
Intra-/extratumoral.
An adverse prognostic indicator.

6. LYMPH NODES

Site/number/size/number involved/limit node/extracapsular spread.
Regional nodes: cystic duct, pericholedochal, hilar, peripancreatic (head), periduodenal, periportal, coeliac, superior mesenteric. A regional lymphadenectomy will ordinarily include a minimum of three lymph nodes.

pN0 no regional lymph node metastasis
pN1 metastasis in regional lymph node(s).

Nodal metastases are usually present at the time of diagnosis with subsequent spread to local structures (liver, pancreas, gall bladder, duodenum), lungs and peritoneal cavity.

7. EXCISION MARGINS

Distances (mm) to the nearest longitudinal and circumferential resection margins of carcinoma and presence of mucosal dysplasia at the longitudinal limits.

Local recurrence usually relates to longitudinal or soft tissue radial margin involvement and is commonest in proximal tumours.

8. OTHER PATHOLOGY

Ninety percent of patients (>60 years, F:M 1 : 1) present with jaundice and diagnosis is by cholangiography (retrograde endoscopic or percutaneous transhepatic) supplemented by FNA/brushings/washings cytology and/or biopsy.

Frozen section diagnosis of bile duct carcinoma can be difficult due to the presence of ductulo-glandular structures in normal bile duct submucosa and the distortion that can occur in inflammatory strictures.

Dysplasia of adjacent bile duct mucosa can have a flat or micropapillary epithelial pattern and must be noted at the resection limits. Intraductal papillary neoplasia or biliary papillomatosis is also a precancerous lesion.

Chronic inflammatory bowel disease (ulcerative colitis), primary sclerosing cholangitis, gall stones and choledochal cysts all show an increased incidence. Radiologically it can be difficult to distinguish between primary sclerosing cholangitis and a stenotic carcinoma.

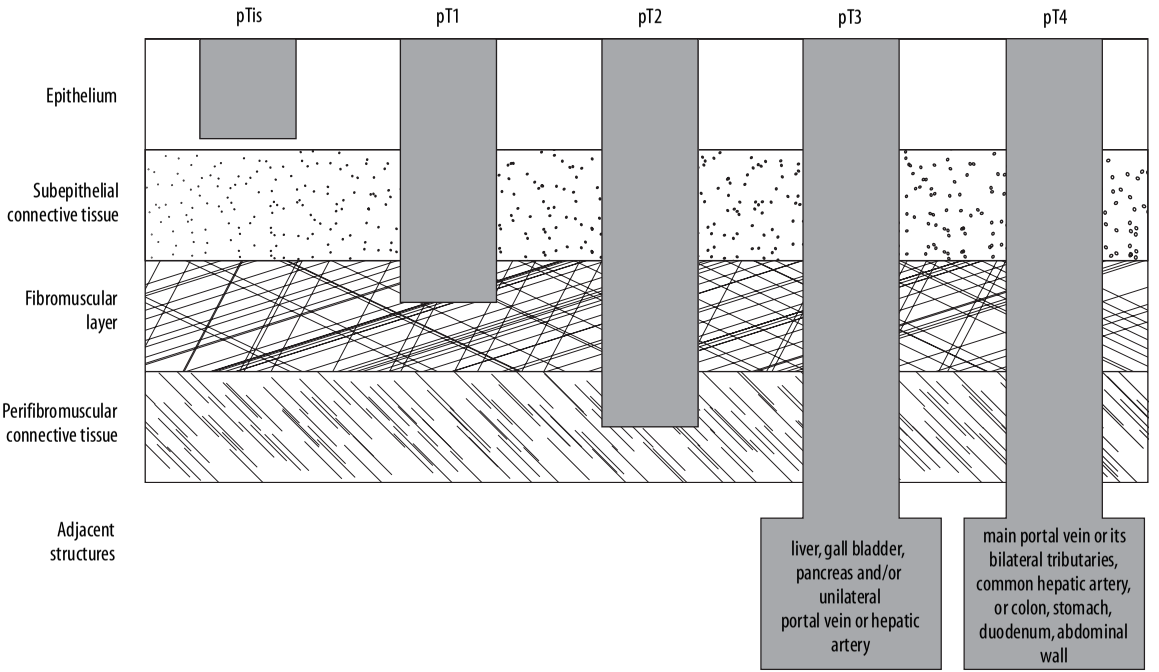


FIGURE 9.2. Extrahepatic bile duct carcinoma.

Immunophenotype
Markers (e.g. cytokeratins, CEA) may be helpful in identifying poorly differentiated single-cell infiltration on biopsy: other markers of bile duct carcinoma are cytokeratins 7 and 19, EMA and CA19-9. There is also overexpression of p53 in contradistinction to normal duct structures. Perineural invasion can point to a diagnosis of malignancy

Prognosis
Prognosis is worse for carcinoma of the upper third and hilum which is diffuse and/or multifocal. Distal lesions that are polypoid or nodular are potentially resectable with better prognosis. Despite being a sclerotic, diffuse tumour, hilar Klatskin lesions have a well-differentiated morphology and indolent time course. Prognosis of bile duct carcinoma is poor with most patients dead within 2–3 years. It relates to tumour location, stage, histological type and grade. Overall survival is 10% with 25% for lesions of the distal third and resectable lesions with negative margins. This can improve to 50–80% 5-year survival if the tumour is ampullary and of early stage (pT1: limited to the sphincter of Oddi). Treatment for proximal lesions (not as high as the hilar plate) is resection (±hepatic lobectomy) with hepatojejunostomy; a Whipple's procedure is indicated for distal lesions. Palliative treatment can involve biliary drainage, stenting or radiotherapy.

9. OTHER MALIGNANCY

Lymphoma/leukaemia
— secondary to systemic/nodal disease.

Sarcoma
— embryonal (botryoid) rhabdomyosarcoma in children with direct invasion of abdominal structures, metastases to bone and lungs and poor prognosis. Desmin/myo D1/myogenin positive small cells, subepithelial cellular cambium layer, deeper myxoid zone.
— leiomyosarcoma, angiosarcoma.

10
Liver Carcinoma

1. GROSS DESCRIPTION

Specimen

— fine needle aspirate/core biopsy/wedge excision/segmentectomy/partial hepatectomy/R/L lobectomy.
— size (cm) and weight (g).

Hepatic resection in malignant disease is potentially considered for

- primary liver tumour involving a single lobe with no invasion of portal vein or inferior vena cava and no significant background cirrhosis.
- isolated metastases (e.g. carcinoid, colorectal carcinoma) localized to a single lobe with no metastatic spread elsewhere and adequate excision of the primary lesion.

Depending on the anatomical extent of disease as determined by MRI/CT/ultrasound scans the resection can be major (partial hepatectomy, lobectomy) or segmental, the latter excised with its supplying lymphovascular pedicle. Note that the surgical definition of lobes and their constituent segments differs from the classical anatomical lobes. Small subcapsular metastases can be removed by wedge resection or erroneously diagnosed as such at frozen section when a bile duct adenoma or Von Meyenberg complex is submitted. Where metastases or a primary hepatocellular carcinoma are potentially resectable or transplant is considered there is a reluctance to carry out FNA/needle biopsy for fear of upstaging the tumour, e.g. needle tract implantation. However, in the absence of a significantly elevated serum alpha-fetoprotein (AFP) or other obvious primary site, needle biopsy (percutaneous or transjugular) may be needed for a firm tissue diagnosis and to exclude other treatable tumours, e.g. malignant lymphoma. Presentation of hepatic malignancy may be with jaundice, weight loss, anaemia and anorexia. There can be a palpable mass and investigations include serum AFP and CA19-9, liver function tests and imaging studies. Metastatic colorectal and pancreatic cancers may have high serum CEA and CA19-9 levels. Needle biopsy yields either a positive diagnosis or the changes adjacent to a mass lesion, i.e. liver plate atrophy, prominent sinusoids and focal inflammation. Transjugular cores are very fine and require careful handling in the

laboratory. However, they can produce useful morphological and immunohistochemical results if the tumour is in a suitably accessible location. Some of the potential upstaging risks are also obviated if a percutaneous route is avoided.

Tumour

Site
— subcapsular/parenchymal/ductocentric/vasculocentric/lobe/multifocal (particularly when cirrhosis is present).

Size
— length × width × depth (cm) or maximum dimension (cm).
— in a cirrhotic liver a lesion >5 cm is probably a hepatocellular carcinoma.

Appearance
— hepatocellular carcinoma: solitary/diffuse/multifocal (particularly in cirrhosis)/bile stained/venous spread/pedunculated/encapsulated/background cirrhosis/haemochromatosis.
— cholangiocarcinoma: papillary/nodular/stenotic/scirrhous/ductocentric/multifocal.
— metastatic carcinoma: single/multiple/necrotic/umbilicated/calcification/diffuse/mucoid/subcapsular.

Edge
— circumscribed/irregular.

2. HISTOLOGICAL TYPE

Hepatocellular carcinoma
— trabecular, plate-like or sinusoidal.
— pseudoglandular (acinar).
— these are the usual types comprising hepatoid cells, bile cytoplasmic staining and canalicular plugging, eosinophilic intranuclear pseudoinclusions, and a sinusoidal vascular pattern with a CD34 positive endothelial lining (capillarization).
— solid (compact): inconspicuous sinusoids.
— scirrhous: fibrotic. Distinguish from cholangiocarcinoma and post-chemo-/radiotherapy changes.
— rarely pleomorphic, clear cell, spindle cell or osteoclast-like.
— variants with good prognosis: fibrolamellar carcinoma (90% <25 years old); pedunculated carcinoma; minute, small or encapsulated carcinoma (see below).

Cholangiocarcinoma (intrahepatic)
— nodular/scirrhous (infiltrative)/intraductal (rare), and, single or multifocal.

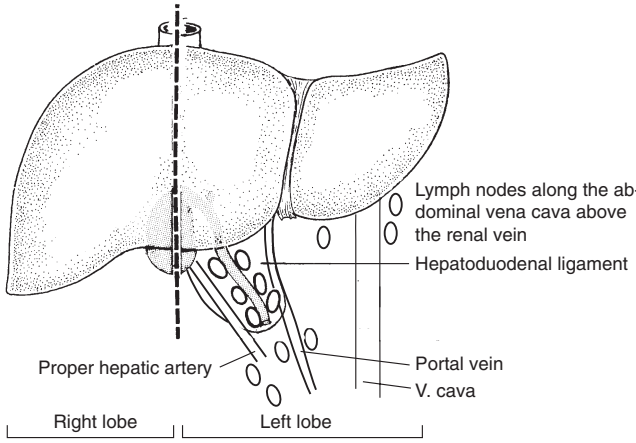


FIGURE 10.1. Liver and regional lymph nodes.

— ductulo-acinar pattern of heterogeneous cuboidal to columnar mucin-secreting cells in a fibrous stroma. Sometimes papillary.
— portal expansion/periportal sleeve-like and parenchymal sinusoidal distributions.
— few survive longer than 2–3 years due to late presentation and limited resectability.
— rarely: mucinous; signet ring cell; adenosquamous; clear cell; pleomorphic; osteoclast-like; spindle cell (sarcomatoid). These are prognostically adverse variants.

Mixed liver cell/bile duct carcinoma

— 1% of cases.

Hepatoblastoma

— 50–60% of childhood liver cancers, 90% <5 years of age.
— usually a large solitary mass and raised serum AFP. Epithelial component of two cell types (fetal/embryonal hepatocytes or small cell anaplastic) and fibrous mesenchyme (25% of cases: osteoid or undifferentiated spindle cells). Treatment is surgery and chemotherapy with a 50–70% long-term survival. Age <1 year, large size and a significant small cell component are adverse factors.

Metastatic carcinoma

— in order of frequency: carcinoma, malignant lymphoma and sarcoma.
— direct spread: stomach, large intestine, pancreas, gall bladder and biliary tree.
— distant spread: stomach, oesophagus, colorectum, lung, breast, malignant melanoma, kidney, urinary bladder, ovary, teratoma.

The tumour distribution may reflect its origin, e.g.

— colorectum: multiple, large nodules with central necrosis and umbilication, ±mucin, ±calcification. As in renal cell carcinoma can be solitary and massive.
— gall bladder: bulk of disease centred on the gall bladder bed.
— lung: medium-sized nodules and fleshy appearance (small cell carcinoma).
— breast, stomach: medium-sized nodules or diffuse cirrhotic-like pattern.
— malignant melanoma: pigmented.
— angiosarcoma, choriocarcinoma, leiomyosarcoma, renal/thyroid carcinoma: haemorrhagic.

NB: carcinoma rarely metastasizes to a cirrhotic liver, i.e. the tumour is more likely to be primary. Histologically there can be considerable difficulty distinguishing hepatocellular carcinoma and its variants from other metastases, e.g. renal cell carcinoma, adrenal cortical carcinoma and malignant melanoma. Similarly, cholangiocarcinoma from gastrointestinal secondaries. Morphology allied to a panel of antibodies should be used, including:

liver—Hep Par 1, AFP, canalicular polyclonal CEA/CD10.
adrenal—inhibin, melan-A, vimentin, synaptophysin.
renal—EMA, vimentin, RCCab, CD10.
colorectal—CK20, CDX-2.
melanoma—S100, HMB-45, melan-A.
GIST—CD34, CD117.

Resection of some hepatic metastases is done to good effect, e.g. carcinoid tumour, colorectal carcinoma.

3. DIFFERENTIATION/GRADE

Well/moderate/poor, or, Grade I/II/III(/IV).

Based on the degree of resemblance to hepatic tissue. Well to moderately differentiated lesions show trabecular (plate-like) or pseudoglandular patterns seen in tumours <2–3 cm diameter. Larger lesions (>3 cm) usually only have a well differentiated periphery with a less differentiated centre characterized by greater cytoarchitectural atypia and no discernable sinusoids. This nodule within nodule appearance is diagnostically useful and highlights the heterogeneity and active evolution of hepatocellular carcinoma. Bile secretion varies.

For cholangiocarcinoma based on the percentage tumour gland formation: well/G1 > 95%; moderate/G2 50–95%; poor/G3 < 50%; undifferentiated/G4 no glands.

4. EXTENT OF LOCAL TUMOUR SPREAD

Border: pushing/infiltrative.
Lymphocytic reaction: prominent/sparse.

The TNM classification applies to hepatocellular carcinoma and intrahepatic cholangiocarcinoma.

pT1 solitary tumour with no vascular invasion
pT2 solitary tumour with vascular invasion or multiple tumours, none >5 cm
pT3 multiple tumours >5 cm or tumour involving a major branch of the portal or hepatic vein(s)

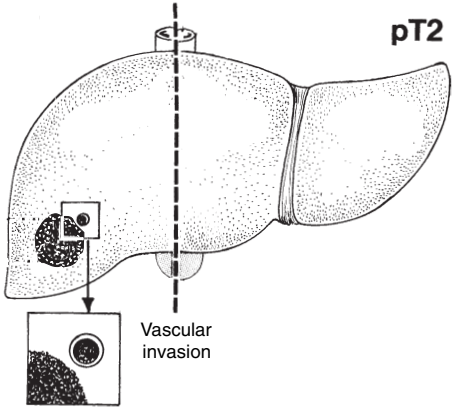


FIGURE 10.2. Liver carcinoma.

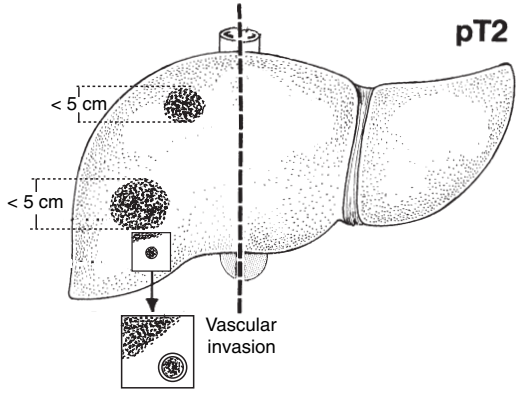


FIGURE 10.3. Liver carcinoma.

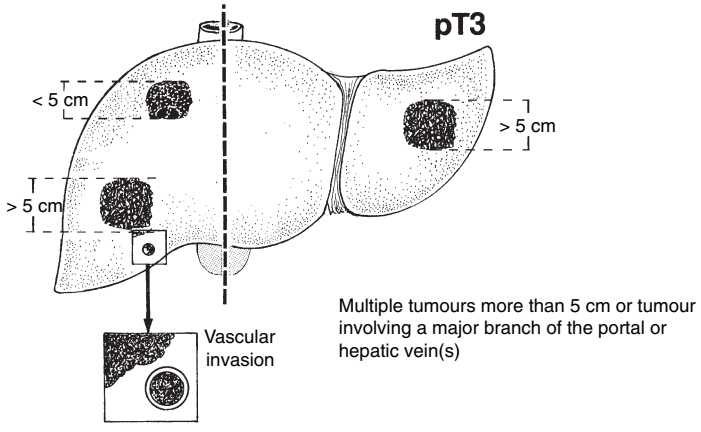


FIGURE 10.4. Liver carcinoma.

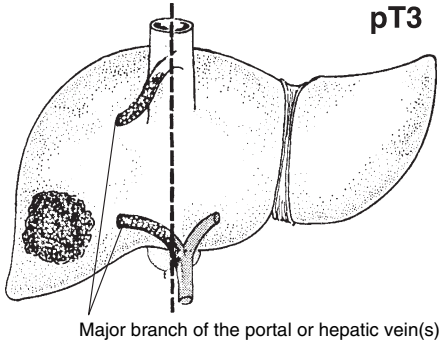


FIGURE 10.5. Liver carcinoma.

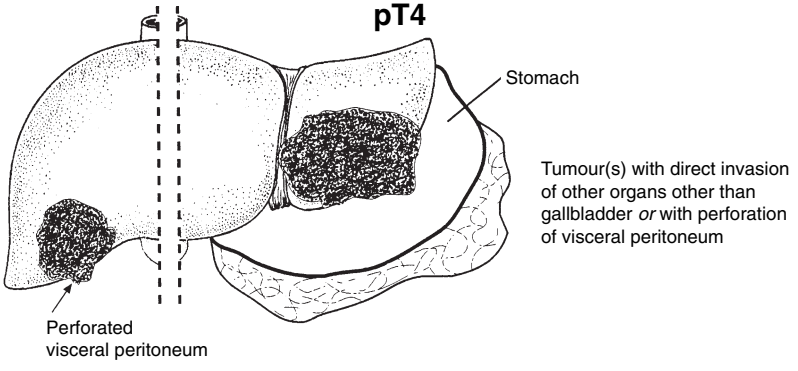


FIGURE 10.6. Liver carcinoma.

pT4 tumour with direct invasion of adjacent organs other than the gall bladder or with perforation of visceral peritoneum.

Vascular invasion is diagnosed by clinical imaging. The pathological classification includes gross and histological involvement.

Multiple tumours includes multiple independent primaries or intrahepatic metastases from a single hepatic carcinoma. Multicentricity is associated with poor prognosis.

5. LYMPHOVASCULAR INVASION

Present/absent.

Intra-/ extratumoral.

Note the particular propensity for hepatocellular carcinoma to involve portal tract veins, major branches of portal and hepatic veins and inferior vena cava, ultimately with metastases to lung, adrenal gland and bone. Cholangiocarcinoma typically shows lymphovascular and perineural invasion with spread to regional lymph nodes, lungs, bone, adrenal gland, kidney, pancreas and peritoneum.

6. LYMPH NODES

Site/number/size/number involved/limit node/extracapsular spread.

Regional nodes: hilar (hepatoduodenal ligament), hepatic (along the hepatic artery), periportal (along portal vein) and those along the inferior vena cava above the renal veins.

pN0 no regional lymph node metastasis
pN1 metastasis in regional lymph node(s).

7. EXCISION MARGINS

Distances (mm) to the serosa and limits of excision of parenchyma, bile ducts and veins.

Mucosal dysplasia at the bile duct excision limits.

8. OTHER PATHOLOGY

Budd–Chiari syndrome secondary to venous invasion

Hepatocellular carcinoma

Risk factors: hepatitis B, C (50–70%, 20–30% of cases respectively, worldwide). Cirrhosis is present in 60–80% of cases in the West secondary to viral hepatitis, alcohol, congenital bile duct atresia, alpha-1-antitrypsin deficiency or haemochromatosis. Small/large cell liver cell dysplasia—there is a strong association between large cell dysplasia and hepatitis B surface antigen. Small cell dysplasia (enlarged nucleus, decreased volume of cytoplasm) is regarded as being a premalignant change and a more important risk factor for development of carcinoma. Adenomatous hyperplastic nodules or macroregenerative nodules in a background of cirrhosis—range from 1 mm diameter to 2–3 cm, ±a fibrous rim, ±cytoarchitectural atypia (plates 3 cells thick, irregular edges, loss of reticulin,

±cellular dysplasia). They show a spectrum of changes towards hepatocellular carcinoma with type 2 (high-grade dysplastic) nodules particularly significant. Increasingly sophisticated imaging is leading to greater detection of these premalignant dysplastic nodules and small, early hepatocellular carcinomas.

Immunophenotype: Hep Par 1, AFP (25%: high specificity but low sensitivity) and polyclonal CEA/CD10 in bile canaliculi. Also CAM5.2 (but not AE1/AE3), cytokeratin 8, 18 (but not 7, 19), ER/PR. PAS-positive cytoplasmic glycogen, intracellular PAS-positive globular inclusions, loss of pericellular reticulin. EMA, Ber EP4 negative.

Cholangiocarcinoma

Risk factors: primary sclerosing cholangitis/ulcerative colitis/liver fluke/biliary tree anomaly. Treatment is surgical (partial/total hepatic resection ± liver transplantation) but prognosis is poor with overall mean survival <2 years.

Immunophenotype: cytokeratins (7, 19), EMA, CEA, CA19-9, mucin positive. Also CAM5.2 (low molecular weight cytokeratins, as for hepatocellular carcinoma) and AE1/AE3 (including high molecular weight cytokeratins, negative in hepatocellular carcinoma).

Differential diagnosis of hepatic mass lesions

Focal nodular hyperplasia: young to middle-aged women, usually solitary and asymptomatic. Radiological and gross central scar with thick-walled vessels, marginal ductular proliferation, plates 2 or 3 cells thick, cirrhosis-like nodule with adjacent normal parenchyma. A vascular anomaly.

Hepatocellular adenoma: middle-aged women with acute abdominal presentation and history of oral contraception. No portal tracts or central veins, liver cell plates ≥2 cells thick with retention of reticulin pattern and sinusoidal Kupffer cells (CD68 positive).

Hepatocellular carcinoma: evidence of risk factors, e.g. cirrhosis. Plates > 2 cells thick, loss of reticulin pattern and Kupffer cells with sinusoid capillarization (CD34), atypia, look for vascular invasion. Serum AFP markedly elevated in 40–75% of cases: CT/MRI scan shows the location of the lesion, its extent of invasion and multicentricity.

Poorly differentiated metastatic carcinoma: specific histological appearance (e.g. small cell carcinoma lung), immunogenicity (e.g. PSA positive) or histochemical feature (e.g. mucin positive—this cannot distinguish secondary adenocarcinoma from primary cholangiocarcinoma).

Sometimes the distinction between a regenerative nodule, adenoma and well-differentiated hepatocellular carcinoma is not possible and the subsequent clinical course establishes the diagnosis. FNA cytology of hepatic mass lesions is useful for simple cysts, abscesses and some metastatic cancers (e.g. small cell lung carcinoma). Secondary adenocar-

cinoma cannot always be distinguished from cholangiocarcinoma and previous history is important, e.g. resection for colorectal carcinoma. Differential cytokeratin expression may help: colorectal cancer (CK20+/CK7–), cholangiocarcinoma (CK7, 19+/CK20±). FNA is reasonably robust for moderately differentiated hepatocellular carcinoma but may need to be supplemented by core/open biopsy in poorly differentiated carcinomas (to exclude metastatic cancers) and well-differentiated lesions (to exclude adenoma, focal nodular hyperplasia, cirrhosis). Useful diagnostic features for hepatocellular carcinoma are: hepatoid cells (polygonal with central nucleus), nuclear/nucleolar enlargement, a trabecular pattern with sinusoidal capillarization, nuclear pseudoinclusions, bile secretion and an absence of bile duct epithelial and inflammatory cells. Immunostaining may also be helpful, e.g. AFP positive.

Prognosis

Treatment of hepatocellular carcinoma depends on surgical resection ± liver transplantation. Chemotherapy is used for recurrent or inoperable tumours. Prognosis relates to tumour size (>5 cm), cell type or differentiation, encapsulation, multifocality, high serum AFP levels, vascular invasion and the presence or absence of a background cirrhosis (an adverse indicator). Five-year survival is at most 10–15% and more usually about 3%. The majority die within several months of presentation with liver failure, haemorrhage and infection. Small tumours (<3–5 cm) and variants such as fibrolamellar and pedunculated carcinoma are potentially curable. Hepatic arterial chemoembolization, percutaneous alcohol injection and radiofrequency ablation also have roles to play with potential survival benefit. These modalities can also be applicable to metastatic deposits in the liver, e.g. colorectal carcinoma.

Fibrolamellar carcinoma

— large eosinophilic cells in a fibrous stroma, potentially resectable.
— 50% cure rate.
— serum AFP not raised, no cirrhosis. May also have areas of usual liver cell carcinoma and cholangiocarcinoma.
— can express CK7, 19.

Pedunculated carcinoma

— inferoanterior aspect right lobe, up to 1 kg weight.

Minute, small encapsulated carcinoma

— 2–5 cm, encapsulated by fibrous tissue.
— 90–100% 5-year survival if no angio-invasion.

9. OTHER MALIGNANCY

Lymphoma/leukaemia

— secondary involvement by Hodgkin's/non-Hodgkin's lymphoma (50–60% of cases) or leukaemia [80% of chronic lymphocytic

leukaemia (CLL)]. Lymphoma is mainly portal and leukaemia sinusoidal but mixed patterns of distribution are common.
— primary lymphoma is rare but of more favourable prognosis—solitary/multiple masses or diffuse and high-grade large B cell in type.

Angiosarcoma
— cirrhosis, PVC (polyvinyl chloride), thorotrast exposure, commonest sarcoma of liver.
— exclude peliosis (well-differentiated angiosarcoma) and primary and secondary carcinoma (poorly differentiated angiosarcoma).
— growth is typically along vascular structures (sinusoids, vessels) and the liver cell plates. The endothelial cells are atypical and CD31/34 positive.

Epithelioid haemangioendothelioma
— multinodular fibrous masses with a zoned periphery of cords and tube-like structures of spindle and epithelioid cells in myxoid stroma and a central hyalinized scar. Cytoplasmic vacuoles, CD31 positive.
— of low to intermediate-grade malignancy: also seen in skin, lung and bone.

Kaposi's sarcoma
— AIDS (15–20% of fatal cases).

Embryonal sarcoma
— 15% 5-year survival in patients of 6–10 years of age.
— spindle/stellate/pleomorphic/rounded cells.

Embryonal rhabdomyosarcoma
— <5 years of age, poor prognosis, desmin/myo D1/myogenin positive small cells.
— arises from major bile ducts near the porta hepatis.

Leiomyosarcoma, fibrosarcoma
— rare.
— exclude sarcomatoid liver carcinoma and more commonly secondary sarcoma, e.g. gastrointestinal stromal tumour.

Carcinoid tumour
— usually represents metastases from gastrointestinal tract. Associated with carcinoid syndrome. Detect by octreotide scan.

Mimics of malignancy
— abscess, sclerosed haemangioma, inflammatory myofibroblastic or pseudotumour (spindle cells in a storiform pattern, plasma cells), angiomyolipoma (fat, vessels, HMB 45 positive spindle cells), solitary fibrous tumour (storiform spindle cells, CD34 positive).

Head and Neck Cancer

- Lip and Oral Cavity Carcinoma
- Oropharyngeal Carcinoma (with comments on nasopharynx and hypopharynx)
- Nasal Cavity and Paranasal Sinus Carcinoma
- Laryngeal Carcinoma
- Salivary Gland Tumours
- Thyroid Gland Tumours (with comments on parathyroid)

General Comments

See: Royal College of Pathologists. Datasets for head and neck carcinoma and salivary neoplasms histopathology reports. London. 2005.

Basic rules are applied to carcinomas arising at various sites in the upper aerodigestive tract (lip, oral cavity, pharynx, nasal cavity, paranasal sinuses and larynx), 95% of which are squamous cell carcinoma.

The surgeon should mark clinically relevant resection margins in the primary specimen and lymph node territories in neck dissections.

Prognosis

Prognosis relates to carcinoma:

Type

— e.g. keratinizing squamous carcinoma vs. undifferentiated naso-pharyngeal carcinoma. This also influences treatment modality, e.g. surgery in the former, chemo-/radiotherapy in the latter.

Grade

— the majority are moderately differentiated but identify well and poorly differentiated lesions. Base on the most aggressive area (medium magnification field).

Size

— maximum diameter (mm): macroscopic or microscopic, whichever is greater.

Depth

— maximum depth of invasion (mm) below the luminal aspect of the surface measured from the extrapolated level of the adjacent mucosa. At least one block per cm diameter of the tumour is required and the whole lesion is submitted if less than 1 cm in maximum dimension.

Invasive edge

— a cohesive vs. non-cohesive pattern of infiltration. The latter equates to single cells, small groups or multiple thin (<15 cells across) strands of cells at the deep aspect of the tumour.

Margins of excision

>5 mm	clear
1–5 mm	close to; also high risk of recurrence if the invasive edge is non-cohesive or shows vascular invasion
<1 mm	involved.

Note also the presence of severe dysplasia at the resection edge.

Lymphovascular and perineural spread

— strong indicators of local recurrence.

Bone invasion

— distinguish erosion of the cortex from infiltration of the medulla.

Lymph node status

— number identified and number involved at each anatomical level of the neck dissection. A typical radial neck dissection without previous chemotherapy or radiotherapy should yield an average of 20 nodes.
— an important prognostic factor is involvement of the lower cervical nodes, that is level IV (lower jugular chain deep to the lower one-third of sternocleidomastoid muscle) and level V (posterior triangle of neck behind the posterior border of sternocleidomastoid).
— maximum dimension of the largest nodal deposit.
— extracapsular spread.
— the significance of micrometastases is uncertain but should be counted as involved.

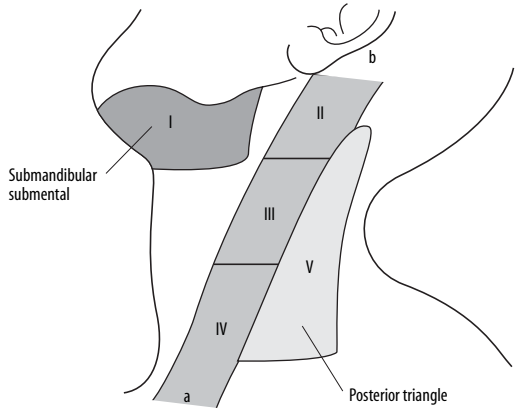


FIGURE 11.A. Lymph node groups in block dissection of the neck.

— persistent cervical lymph node enlargement in an older patient is commonly malignant due to either lymphoma or metastases. The latter are generally due to head and neck tumours, particularly mucosal squamous cell carcinomas, malignant melanoma of skin and thyroid gland carcinoma. Pharyngeal and laryngeal lesions should also be considered and once a tissue diagnosis has been obtained by FNA, panendoscopy of the upper aerodigestive tract is undertaken to establish the primary site. CT, MRI scan and thyroid ultrasound are also used for investigation and staging. A small minority (10%) can be due to non-head and -neck lesions, e.g. lung, stomach, prostate or testis. Patients can present with their metastatic disease, the occult primary being in the nasopharynx, posterior one-third of tongue, tonsil or hypopharynx. Neck dissection is either therapeutic (to remove metastases) or elective in a clinically negative neck to avoid any such future possibility. This decision will depend on the risk factors present, age, and fitness of the patient. Extent of resection relates to the tumour type, site and expected pattern of spread and is usually more limited (selective neck dissection, e.g. levels I–II or II–IV) in elective cases. Therapeutic dissection (radical or modified radical, levels I–V ± sternomastoid, internal jugular vein, spinal accessory nerve and submandibular gland) aims to give maximum disease clearance where there are large (>6 cm), multiple deposits, extranodal spread or recurrent disease. Positive lymph nodes (≥2) in the resection warrant postoperative radiotherapy. Head and neck cancer specimens should also be interpreted in the light of any previous radiotherapy or chemotherapy due to potential morphological alterations and tumour regression that may make accurate staging more difficult.

11

Lip and Oral Cavity Carcinoma

1. GROSS DESCRIPTION

Specimen

— fine needle aspirate/diagnostic or (wedge) excision biopsy/resection, e.g. glossectomy/neck dissection.
— size (cm) and weight (g).
— pathological lesions present either as a lump, ulcer, red or white mucosal patch and require biopsy to determine their nature.
— preoperative investigation of a mass will include plain X-ray, MRI and CT scan to assess local spread, bone destruction and/or cervical nodal metastases. Local wedge excision (± shave excision of adjacent mucosa) is used for small tumours of the lip and tip/lateral border of tongue, hemiglossectomy for deeply infiltrative cancers and (sub)total glossectomy for large tumours crossing the midline or involving the posterior one-third. Sublingual gland is submitted with anterior floor of mouth lesions and superficial gingival tumours require mucosal excision only. Periosteum acts as a barrier to bone spread but where it is demonstrated radiologically rim or hemimandibulectomy may be required. Previous irradiation can disrupt the periosteum increasing bone spread. Adequate demonstration will require decalcification with the overlying soft tissues in place. Where there is proven or likely nodal metastases an en bloc neck dissection is performed.

Tumour

Site

— lip: external upper.
external lower.
commissures.

When the skin is involved if >50% of the tumour is within the vermillion border the tumour is designated as lip in origin.

— oral cavity:
buccal mucosa—lips/cheek/retromolar areas/bucco-alveolar sulci.
upper alveolus and gingiva (upper gum).
lower alveolus and gingiva (lower gum).

hard palate.
tongue—dorsal surface and lateral borders (anterior two-thirds); inferior (ventral) surface.
floor of mouth.

The commonest sites are, in order of decreasing frequency, lip (90% lower), lateral borders of tongue (35%), anterior floor of mouth (20%) and the soft palate complex (soft palate, anterior pillar of fauces and retromolar areas).

Multifocal lesions are not uncommon (10%), both synchronous and metachronous.

Size
— length × width × depth (cm) or maximum dimension (cm).

Appearance
— verrucous/warty/nodular/sessile/plaque/ulcerated.

Edge
— circumscribed/irregular.

2. HISTOLOGICAL TYPE

Squamous cell carcinoma
— 90% of cases.
— keratinizing/non-keratinizing.

variants:

— verrucous: elderly, tobacco usage, broad based exophytic and "church spire" hyperkeratosis with a pushing deep margin of cytologically bland bulbous processes. Locally invasive (75% 5-year survival) but may become aggressive after radiotherapy.
— papillary: >70% exophytic or papillary malignant epithelial fronds with focal invasion at the base (70% 5-year survival).
— spindle cell: polypoid and pleomorphic, cytokeratin (AE1/AE3—70%) positive, distinguish from sarcoma. A more obvious in-situ or invasive squamous component may be seen and nodal metastases can show a spectrum of epithelial and spindle cell changes. Prognosis (80% 5-year survival) relates to the depth of invasion.
— basaloid: poor prognosis, nests of palisaded basaloid cells with central comedonecrosis, hyalinised stroma.
— adenoid squamous: usual prognosis, acantholytic (pseudoglandular) pattern.
— adenosquamous: poor prognosis, mixed differentiation squamous carcinoma and adenocarcinoma (either obvious glands or solid with mucin positive cells).

Salivary gland tumours
— there is a higher frequency in the oral cavity (particularly palate) of carcinoma of minor salivary gland origin, e.g. polymorphous low-

grade adenocarcinoma (cytological uniformity with architectural diversity), adenoid cystic carcinoma, mucoepidermoid carcinoma, acinic cell carcinoma, carcinoma ex pleomorphic adenoma.

Small cell carcinoma
— aggressive: pure or with a squamous component. Chromogranin/synaptophysin/CD56/paranuclear dot CAM5.2 positive.

Malignant melanoma
— Japanese/Africans, palate and gingiva, ± adjacent junctional activity. Prognosis is poor with nodal and distant metastases common.
— lip: desmoplastic melanoma. Show S100 positivity to distinguish from fibrous tissue; ± neurotropism. Can be negative for HMB-45 and melan-A.

Metastatic carcinoma
— lung, breast, kidney, gut, malignant melanoma or direct spread from nasal cavity/maxillary sinus.

3. DIFFERENTIATION
Well/moderate/poor/undifferentiated, or Grade 1/2/3/4.

— for squamous carcinoma based on cellular atypia, keratinization and intercellular bridges.
— usually moderately differentiated, whereas carcinomas at the base of the tongue can be poorly differentiated/undifferentiated and immunohistochemistry for cytokeratins is needed to distinguish from malignant lymphoma.
— undifferentiated carcinoma is grade 4.
— most salivary gland tumours are graded according to type, e.g. acinic cell carcinoma and polymorphous low-grade adenocarcinoma are low grade but salivary duct and undifferentiated carcinoma are high grade.

4. EXTENT OF LOCAL TUMOUR SPREAD
Border: pushing/infiltrative.
Lymphocytic reaction: prominent/sparse.
The TNM classification applies to carcinomas of the lip and oral cavity including those of minor glands.

pTis	carcinoma in situ
pT1	tumour ≤ 2 cm in greatest dimension
pT2	tumour > 2 cm but ≤ 4 cm in greatest dimension
pT3	tumour > 4 cm in greatest dimension
pT4a	Lip: tumour invades adjacent structures, e.g. through cortical bone, inferior alveolar nerve, floor of mouth, skin (chin or nose) Oral cavity: tumour invades adjacent structures, e.g. through cortical bone, into deep (extrinsic) muscle of tongue, maxillary sinus, skin of face

pT4b Lip and oral cavity: tumour invades masticator space, pterygoid plates, or skull base, or encases internal carotid artery.

Cancers of the lip and lateral borders of the tongue may remain localized for considerable periods of time prior to invasion of local adjacent structures.

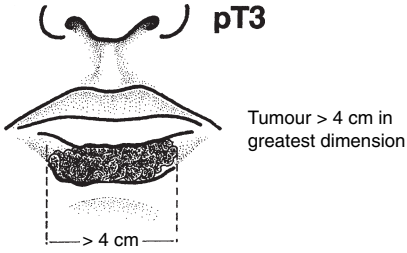


FIGURE 11.1. Lip and oral cavity carcinoma.

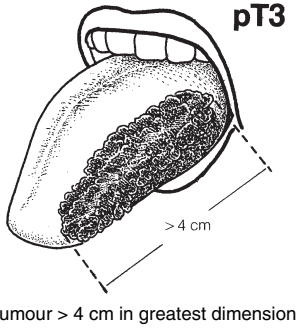


FIGURE 11.2. Lip and oral cavity carcinoma.

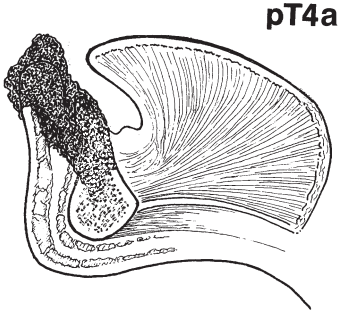


FIGURE 11.3. Lip and oral cavity carcinoma.

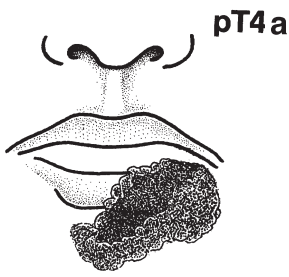


FIGURE 11.4. Lip and oral cavity carcinoma.

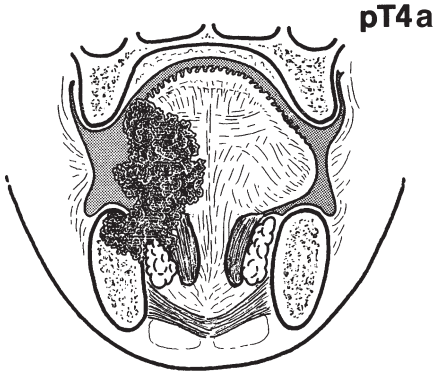


FIGURE 11.5. Lip and oral cavity carcinoma.

Distinguish tumour extending to or overlying bone from gross erosion or radiographic destruction of bone.

5. LYMPHOVASCULAR INVASION

Present/absent.
Intra-/extratumoral.
Perineural spread: predictor of local recurrence.

6. LYMPH NODES

Metastases are mainly lymphatic with the more anterior the tumour the lower the position of the cervical nodes involved. Nodal metastases may also undergo cystic degeneration with central straw-coloured fluid and viable cells at the tumour margin only. Residual paucicellular masses of keratin with a foreign body reaction may result from radiation therapy. These features should be borne in mind on FNA of cervical nodes and a

careful search made for malignant cells, which may be very well differentiated. A common differential diagnosis is branchial cyst.

Site/number/size/number involved/limit node/extracapsular spread.

Regional nodes: cervical.

Level I:	submental, submandibular
Level II:	upper jugular
Level III:	middle jugular
Level IV:	lower jugular
Level V:	posterior triangle

A selective neck dissection will ordinarily include a minimum of six lymph nodes, a (modified) radical dissection 10 lymph nodes.

pN0	no regional lymph node metastasis
pN1	metastasis in a single ipsilateral node ≤ 3 cm
pN2	metastasis in:
	a. ipsilateral single node > 3 cm to 6 cm
	b. ipsilateral multiple nodes ≤ 6 cm
	c. bilateral, contralateral nodes ≤ 6 cm
pN3	metastasis in a lymph node > 6 cm.

Extracapsular extension: present/absent. Increases the risk of local recurrence and distant spread. Metastasis is usually to ipsilateral nodes but lesions of the tip of the tongue, those that cross the midline or the posterior one-third can cause contralateral node involvement.

7. EXCISION MARGINS

Distances (mm) of tumour to the nearest painted excision margins.
Epithelial dysplasia/carcinoma in situ present at excision margins.
An ideal therapeutic margin is 10 mm but often resections afford only 2–3 mm which is compounded by a peritumoral zone of dysplastic or hypertrophic mucosa.

8. OTHER PATHOLOGY: PREDISPOSING FACTORS

Gender (M:F 2:1), smoking and alcohol are the main risk factors.

Clinical

leukoplakia	thin, smooth	⇩ cancer risk rises
	thick, fissured	
	granular, verruciform	
	erythroleukoplakia 25–33% risk	
erythroplakia	50% cancer risk.	

Histological: dysplasia

— mild/moderate/severe. Most clinical examples of leukoplakia do not show histological dysplasia, although if present it indicates a greater predisposition to carcinoma. Note that carcinoma can also arise from lesions with no dysplasia.

Others
— smokeless tobacco keratosis.
— chronic hyperplastic candidosis. This may also mimic squamous carcinoma histologically and treatment of infection is advised prior to any designation of malignancy.
— human papilloma virus (HPV 16, 18): aetiological factor contributing to verrucous and squamous carcinoma.
— smoking, alcohol, post-transplant immunosuppression.

Squamous carcinoma is positive for a range of cytokeratins (excluding CK 20 and CAM5.2) and this is of use in the distinction of spindle cell carcinoma from sarcoma.

Prognosis
Prognosis relates to tumour site, stage and histological grade.

lip	90% 5-year survival
anterior tongue	60% 5-year survival (20 % with large tumours and positive nodes)
posterior tongue, floor of mouth	40% 5-year survival.

Treatment is by surgery and/or radiotherapy supplemented by chemotherapy depending on the site and stage of disease.

9. OTHER MALIGNANCY

Lymphoma
— Waldeyer's ring is the commonest site of oropharyngeal non-Hodgkin's lymphoma but it can arise in gingiva, buccal mucosa and palate. Most are B cell and diffuse, although others, e.g. T-cell non-Hodgkin's lymphoma (NHL) and anaplastic large cell lymphoma, do occur. Some are MALT derived and associated with extranodal lymphomas elsewhere, e.g. stomach, whereas others are of nodal type, e.g. mantle cell. Prognosis relates to histological type and grade and stage of disease. There is an increasing incidence with AIDS.

Leukaemia
— direct infiltration or ulceration with opportunistic infection, e.g. herpes simplex virus, cytomegalovirus. Gingival involvement is seen in 4% of acute myeloid leukaemia. Rarely granulocytic sarcoma (CD68/chloroacetate esterase/myeloperoxidase positive) is the first presentation of disease.

Plasmacytoma/myeloma
κ, λ light chain restriction. Look for evidence of systemic disease, e.g. serum immune paresis and monoclonal gammopathy, Bence-Jones proteinuria, radiological lytic bone lesions.

Odontogenic/osseous cancers by direct spread

Sarcoma

— Kaposi's sarcoma: AIDS, palate.
— leiomyosarcoma: cheek.
— rhabdomyosarcoma: embryonal—children soft palate, desmin/myo D1/myogenin positive.
— synovial sarcoma: young adults, cheek, tongue, palate.

Granular cell tumour

— a benign nerve sheath tumour composed of S100 positive granular cells. Commonly, overlying pseudoepitheliomatous hyperplasia can mimic squamous cell carcinoma and a careful search for granular cells in the biopsy subepithelial connective tissues must be made.

12

Oropharyngeal Carcinoma (with comments on nasopharynx and hypopharynx)

1. GROSS DESCRIPTION

Specimen

— fine needle aspirate/biopsy/tonsillectomy/adenoidectomy/pharyngectomy/pharyngooesophagectomy ± laryngectomy/neck dissection.
— weight (g) and size (cm), number of fragments.

Depending on the anatomical site of the lesion, patients can present with dysphagia, hoarseness, deafness, cranial nerve palsy or cervical lymphadenopathy. Investigation is by endoscopy with biopsy and cervical node FNA to obtain a diagnosis. CT and MRI scan are used to assess local tumour spread and metastasis to the neck and elsewhere. Chest X-ray can detect concurrent lung cancer. Extent of resection depends on tumour site, stage, lymph node spread, fitness of the patient and any concurrent tumour. Tonsil is submitted when there is asymmetrical enlargement or as a possible site of an occult primary in FNA-proven cervical node metastases. Carcinoma in the post nasal space is a not infrequent source.

Tumour

Site

Oropharynx: lies between the soft palate and tip of the epiglottis. Most tumours arise in the posterior third of tongue and the tonsil.
Boundaries:

1. anterior wall	posterior third tongue, vallecula
2. lateral wall	tonsil, tonsillar fossa and pillars
3. posterior wall	
4. superior wall	inferior surface soft palate, uvula.

Nasopharynx (post nasal space): superiorly from the skull base and delineated inferiorly by the superior surface of the soft palate.

Hypopharynx: delineated anteriorly by the larynx and aryepiglottic folds, laterally the piriform sinus and superiorly the oropharynx at the level of the hyoid bone. It lies below the tip of the epiglottis down to the start of the oesophagus at the postcricoid area. The majority (75%) of tumours arise in the piriform fossa.

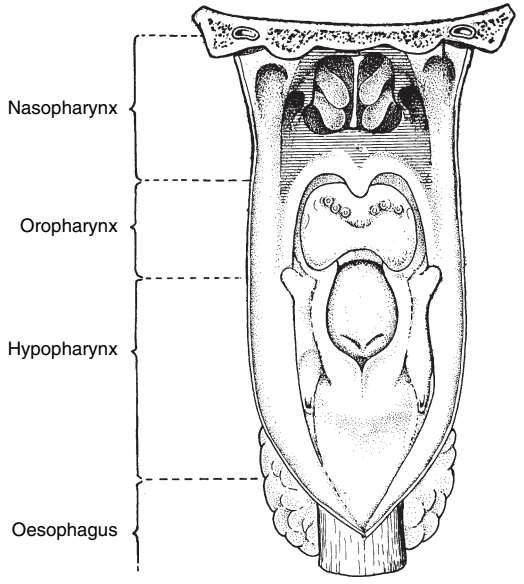


FIGURE 12.1. Pharynx.

Size
— length × width × depth (cm) or maximum dimension (cm).

Appearance
— polypoid/sessile/ulcerated/fleshy.

Edge
— circumscribed/irregular.

2. HISTOLOGICAL TYPE

Squamous cell carcinoma
— 80% of cases and predominantly well-differentiated keratinizing.
— keratinizing/non-keratinizing.

variants:

— verrucous: elderly, tobacco usage, broad based exophytic and "church spire" hyperkeratosis with a pushing deep margin of cytologically bland bulbous processes. Locally invasive (75% 5-year survival) but may become aggressive after radiotherapy.
— papillary: >70% exophytic or papillary malignant epithelial fronds with focal invasion at the base (70% 5-year survival).

— spindle cell: polypoid and pleomorphic, cytokeratin (AE1/AE3—70%) positive, distinguish from sarcoma. A more obvious in-situ or invasive squamous component may be seen and nodal metastases can show a spectrum of epithelial and spindle cell changes. Prognosis (80% 5-year survival) relates to the depth of invasion.
— basaloid: poor prognosis, nests of palisaded basaloid cells with central comedonecrosis, hyalinised stroma.
— adenoid squamous: usual prognosis, acantholytic (pseudoglandular) pattern.
— adenosquamous: poor prognosis, mixed differentiation squamous carcinoma and adenocarcinoma (either obvious glands or solid with mucin positive cells).
— "transitional type": 10%. Features intermediate between squamous and "transitional cell" carcinoma with variable keratinization and differentiation.

Undifferentiated carcinoma
— 15%.
— absence of squamous or glandular differentiation.
— particularly nasopharynx where it is EBV related and associated with a prominent lymphocytic component (lymphoepithelioma).

Salivary gland tumours
— adenoid cystic carcinoma.
— acinic cell carcinoma.
— mucoepidermoid carcinoma.
— polymorphous low grade adenocarcinoma.

Malignant melanoma
— primary or secondary, poor prognosis.

Neuroendocrine carcinoma
— carcinoid/atypical carcinoid/small cell carcinoma.

Metastatic carcinoma
— renal cell carcinoma, breast, lung, gut.

3. DIFFERENTIATION
Well/moderate/poor/undifferentiated, or Grade 1/2/3/4.

— for squamous carcinoma based on cellular atypia, keratinization and intercellular bridges.
— undifferentiated carcinoma is grade 4.
— mainly well-differentiated keratinizing but varies according to tumour site, e.g. nasopharyngeal carcinoma is of undifferentiated type. Carcinoma of the tonsil and base of the tongue also tends to be poorly differentiated.
— most salivary gland tumours are graded according to type, e.g. acinic cell carcinoma and polymorphous low-grade adenocarcinoma are

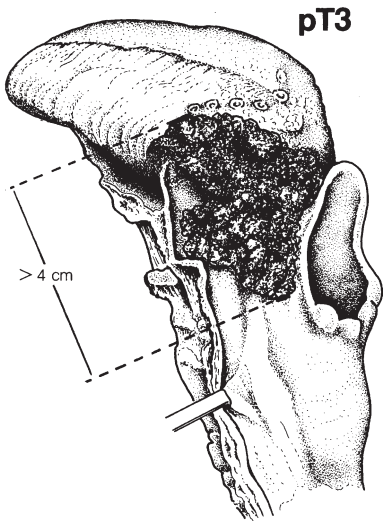


FIGURE 12.2. Oropharyngeal carcinoma.

low-grade but salivary duct and undifferentiated carcinoma are high-grade.

4. EXTENT OF LOCAL TUMOUR SPREAD

Border: pushing/infiltrative.
Lymphocytic reaction: prominent/sparse.
The TNM classification applies only to carcinomas.

Oro-(hypopharynx)

pT1	tumour ≤ 2 cm in greatest dimension (hypopharynx—and limited to one subsite)	
pT2	2 cm < tumour ≤ 4 cm in greatest dimension (hypopharynx—and more than one subsite or adjacent site, without fixation of hemilarynx)	
pT3	tumour > 4 cm in greatest dimension (hypopharynx—or with fixation of hemilarynx*)	
pT4	tumour invades any of	
	oropharynx	4a: larynx, deep/extrinsic muscle of tongue†, medial pterygoid, hard palate, and mandible

*Fixation of hemilarynx is diagnosed endoscopically by immobility of the arytenoid or vocal cord.
†Invasion of deep muscle of tongue is usually associated with restriction of tongue mobility clinically.

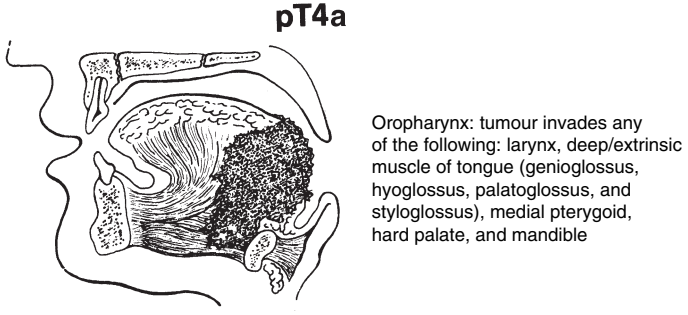


FIGURE 12.3. Oropharyngeal carcinoma.

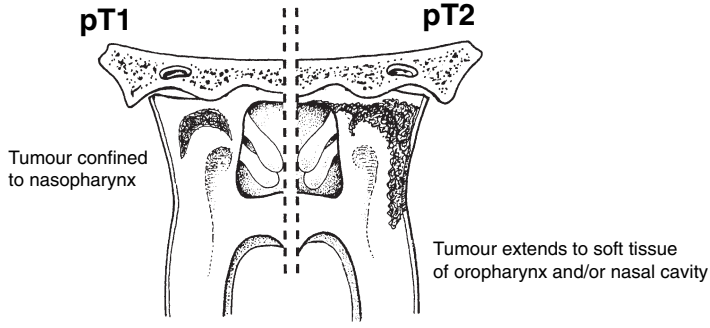


FIGURE 12.4. Nasopharyngeal carcinoma.

4b: lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base, or encases carotid artery.

hypopharynx
4a: thyroid/cricoid cartilage, hyoid bone, thyroid gland, oesophagus, central compartment soft tissue (including prelaryngeal strap muscles and subcutaneous fat)
4b: prevertebral fasia, encases carotid artery, or invades mediastinal structures.

Nasopharynx

pT1 tumour confined to nasopharynx
pT2 tumour into oropharynx and/or nasal fossa without/with (2a/2b) parapharyngeal extension
pT3 tumour into bone and/or nasal sinuses
pT4 intracranial extension and/or into cranial nerves, hypopharynx, orbit, infratemporal fossa, or masticator space.

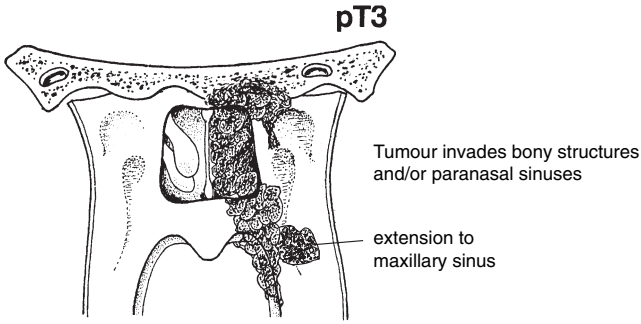


FIGURE 12.5. Nasopharyngeal carcinoma.

5. LYMPHOVASCULAR INVASION

Present/absent.
Intra-/extratumoral.

6. LYMPH NODES

Site/number/size/number involved/limit node/extracapsular spread.
Regional nodes: cervical

Level I:	submental, submandibular
Level II:	upper jugular
Level III:	middle jugular
Level IV:	lower jugular
Level V:	posterior triangle

A selective neck dissection will ordinarily include a minimum of six lymph nodes, a (modified) radical dissection 10 lymph nodes.

Oro- and hypopharynx

pN0 no regional lymph node metastasis
pN1 metastasis in a single ipsilateral node ≤ 3 cm
pN2 metastasis in
  a. ipsilateral single node > 3 cm to 6 cm
  b. ipsilateral multiple nodes ≤ 6 cm
  c. bilateral, contralateral nodes ≤ 6 cm
pN3 metastasis in a lymph node > 6 cm.

Nasopharynx

pN1 unilateral nodal metastasis ≤ 6 cm, above supraclavicular fossa
pN2 bilateral nodal metastasis ≤ 6 cm, above supraclavicular fossa
pN3 metastasis in (a) nodes > 6 cm or (b) in supraclavicular fossa.

Presentation in up to 10% of cases is with upper cervical lymph node metastases mimicking malignant lymphoma. Cervical metastases of nasopharyngeal carcinoma may also show a necrotizing granulomatous

nodal reaction. Carcinomas of the base of the tongue and oropharynx tend to metastasize to the retropharyngeal nodes and rarely (6%) the posterior triangle of neck.

7. EXCISION MARGINS

Distances (mm) to the nearest longitudinal and circumferential excision margins.

Due to anatomical limitations on resection, margins are usually only several millimetres.

8. OTHER PATHOLOGY

Concurrent carcinoma bronchus, oropharyngolaryngeal ring: 10–15%.

Primary treatment of oropharyngeal and hypopharyngeal carcinoma is surgical ± adjuvant radio-/chemotherapy, with the majority of lesions being well-differentiated keratinizing squamous cell carcinoma. In contrast, primary treatment of nasopharyngeal carcinoma is radio-/chemotherapy. A majority of nasopharyngeal carcinomas are of undifferentiated type comprising a syncytial arrangement of enlarged tumour cells with a prominent nucleolus and an accompanying lymphoid stroma. The tumour is strongly associated with EBV infection, which can be shown by immunohistochemistry [EBV LMP (latent membrane protein)] or in-situ hybridization techniques. Serum EBV levels are also useful for monitoring the effects of treatment and detecting recurrence. Markers are helpful in distinguishing carcinoma (cytokeratins, EMA) from high-grade lymphoma (CD45) and malignant melanoma (S100, HMB-45, melan-A). Nasopharyngeal carcinoma has a biphasic age presentation (15–25 years, 60–90 years) with the keratinizing squamous cell variant (not EBV related) occurring in the older age group. Nasopharynx has separate pT and pN staging in the TNM system. Hypopharynx may also be submitted with a laryngectomy specimen due to spread from a laryngeal carcinoma.

Prognosis

Prognosis of oropharyngeal carcinoma relates to tumour site, stage and histological grade, with 20–40% 5-year survival rates for the posterior tongue, tonsil and palate. Undifferentiated carcinoma has a very poor prognosis. However, the chemo-/radiosensitivity of nasopharyngeal carcinoma results in complete remission in 80% of cases and 10-year survival rates of 40%. The keratinizing squamous cell variant in the older age group is of worse prognosis, as are cancers with lower cervical rather than upper cervical lymph node metastases.

9. OTHER MALIGNANCY

Leukaemia

Lymphoma

— large B cell non-Hodgkin's lymphoma.
— mantle cell lymphoma: intermediate-grade and aggressive.

— MALToma with recurrence in other MALT sites, e.g. stomach, Waldeyer's ring.
— angiocentric T-cell lymphoma: aggressive.

Plasmacytoma/myeloma

κ, λ light chain restriction. Look for evidence of systemic disease, e.g. serum immune paresis and monoclonal gammopathy, Bence–Jones proteinuria, radiological lytic bone lesions.

Sarcoma

— children: embryonal rhabdomyosarcoma (subepithelial cellular cambium layer; deeper myxoid zone; desmin/myo D1/myogenin positive).
— young adults: synovial sarcoma; pharynx, palate.
— Kaposi's sarcoma: AIDS.

Nasopharyngeal chordoma (locally destructive), olfactory neuroblastoma, primitive neuroectodermal tumour

13

Nasal Cavity and Paranasal Sinus Carcinoma

1. GROSS DESCRIPTION

Specimen

— fine needle aspirate/biopsy/resection, e.g. rhinectomy, maxillectomy, ethmoidectomy, craniofacial resection/neck dissection.
— weight (g) and size (cm), number of fragments.

Clinical presentation is with nasal obstruction, rhinorrhoea, epistaxis or facial pain. Investigation is by endonasal endoscopy with biopsy. Plain X-ray, CT and MRI scan can demonstrate and stage a soft tissue mass and any bone destruction. Tumour can be removed piece-meal by fibre-optic endoscopic (sinus) surgery (FE(S)S) or more formal resection used. Nasal septal lesions are excised via a lateral rhinotomy. Medial maxillectomy is the commonest procedure for low-grade tumours of the lateral nasal cavity, or maxillary, ethmoid and frontal sinuses, e.g. transitional papilloma or olfactory neuroblastoma. Craniofacial resection is for aggressive tumours or those of the frontal or ethmoid sinus that extend into the anterior cranial fossa. Orbital exenteration may be required if there is involvement of its bony wall. Neck dissection is carried out when there are proven metastases. These are complex specimens and they require careful marking by and liaison with the surgeon.

Tumour

Site

— nasal cavity, maxillary sinus, ethmoid sinus, sphenoid/frontal sinuses.
— maxillary and ethmoid sinuses are the commonest tumour sites.
— mucosal/osseous/extrinsic.

Size

— length × width × depth (cm) or maximum dimension (cm).

Appearance

— exophytic/papillary/mucoid/sclerotic/chondroid/osseous.

Edge

— circumscribed/irregular.

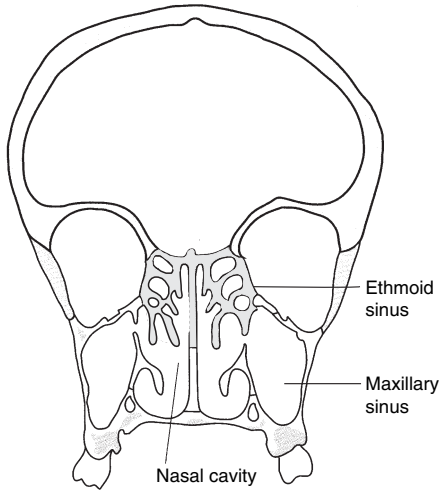


FIGURE 13.1. Paranasal sinuses.

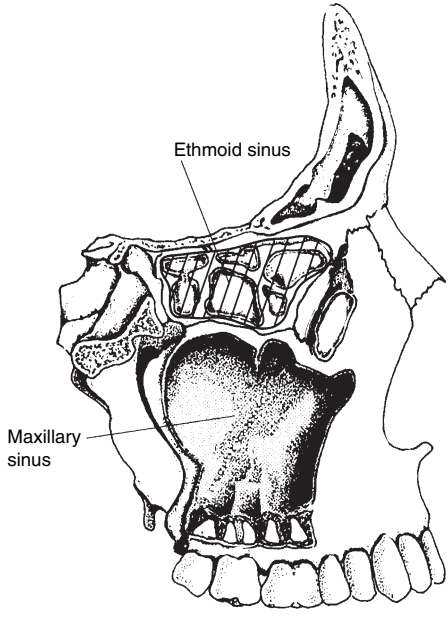


FIGURE 13.2. Paranasal sinuses.

2. HISTOLOGICAL TYPE

Squamous cell carcinoma
— 85% of cases of sinonasal carcinoma.
— keratinizing/non-keratinizing.
— usually moderately differentiated keratinizing.

variants:

— verrucous: elderly, tobacco usage, broad based exophytic and "church spire" hyperkeratosis with a pushing deep margin of cytologically bland bulbous processes. Locally invasive (75% 5-year survival) but may become aggressive after radiotherapy.
— papillary: >70% exophytic or papillary malignant epithelial fronds with focal invasion at the base, 70% 5-year survival.
— spindle cell: polypoid and pleomorphic, cytokeratin (AE1/AE3—70%) positive, distinguish from sarcoma. A more obvious in-situ or invasive squamous component may be seen and nodal metastases can show a spectrum of epithelial and spindle cell changes. Prognosis (80% 5-year survival) relates to the depth of invasion.
— basaloid: poor prognosis, nests of palisaded basaloid cells with central comedonecrosis, hyalinised stroma.
— adenoid squamous: usual prognosis, acantholytic (pseudoglandular) pattern.
— adenosquamous: poor prognosis, mixed differentiation squamous carcinoma and adenocarcinoma (either obvious glands or solid with mucin positive cells).
— "transitional type": possible origin in Schneiderian papilloma which is a benign but locally recurrent sinonasal tumour. A papillary exophytic or inverted growth pattern neoplasm with features intermediate between transitional and squamous epithelia. Complicated by carcinoma in 3% of cases, which is either focal (good prognosis) or diffusely infiltrative (25% survival rate). Variable keratinization and differentiation.

Undifferentiated carcinoma
— absence of squamous or glandular differentiation.
— particularly nasopharynx where it is EBV related and associated with a prominent lymphocytic component (lymphoepithelioma).
— cytokeratin/EMA positive.

Carcinoid/atypical carcinoid/small cell carcinoma/sinonasal neuroendocrine carcinoma

Adenocarcinoma
— papillary.
— polypoid/well-differentiated intestinal pattern/woodworker's tumour (wood dust exposure)/middle turbinate or ethmoid sinus/locally aggressive and recurrent. Prognosis related to the degree of glandular differentiation.

— mucoepidermoid carcinoma.
— acinic cell carcinoma.
— adenoid cystic carcinoma.
— adenocarcinoma of no specific type.

Malignant melanoma
— rare (commoner in nasal cavity), 2% of malignant paranasal tumours, antrum, ethmoid, frontal sinuses.
— ± adjacent mucosal junctional activity.
— poor prognosis (most dead within 5 years).

Metastatic carcinoma
— renal, lung, breast, gut, malignant melanoma.

3. DIFFERENTIATION
Well/moderate/poor/undifferentiated, or Grade 1/2/3/4.
— for squamous carcinoma based on cellular atypia, keratinization and intercellular bridges.
— the majority are moderately differentiated but this varies according to tumour site and type, e.g. undifferentiated nasopharyngeal carcinoma (grade 4).
— for adenocarcinoma based on the percentage tumour gland formation (well/G1 > 95%; moderate/G2 50–95%; poor/G3 < 50%; undifferentiated/G4 no glands).

4. EXTENT OF LOCAL TUMOUR SPREAD
Border: pushing/infiltrative.
Lymphocytic reaction: prominent/sparse.
The TNM classification applies only to carcinomas.

pTis carcinoma in situ.

Maxillary sinus
pT1 tumour limited to the antral mucosa
pT2 tumour causes erosion or destruction of bone (including extension into hard palate and/or middle nasal meatus), except posterior antral wall and pterygoid plates
pT3 tumour invades any of: posterior wall maxillary sinus, subcutaneous tissues, floor/medial wall orbit, pterygoid fossa, ethmoid sinus(es)
pT4 tumour invades or any of:
4a: anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
4b: orbital apex, dura, brain, middle cranial fossa, cranial nerves (other than maxillary division trigeminal nerve V2), nasopharynx, clivus.

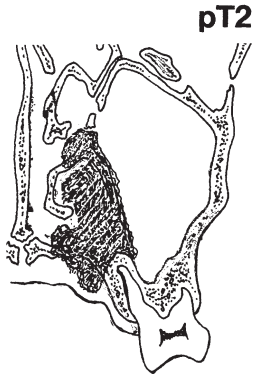


FIGURE 13.3. Maxillary sinus carcinoma.

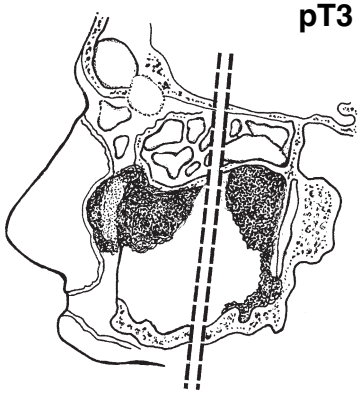


FIGURE 13.4. Maxillary sinus carcinoma.

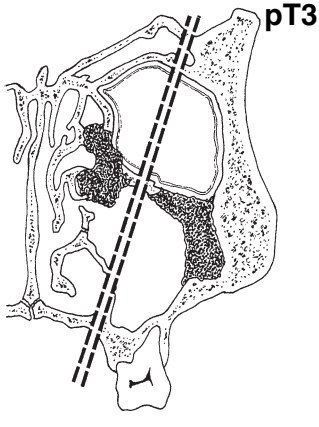


FIGURE 13.5. Maxillary sinus carcinoma.

Nasal cavity and ethmoid sinus

pT1 tumour confined to one subsite of nasal cavity or ethmoid ± bone invasion

pT2 tumour involves two subsites in a single site or extends to involve an adjacent site within the nasoethmoidal complex ± bone invasion

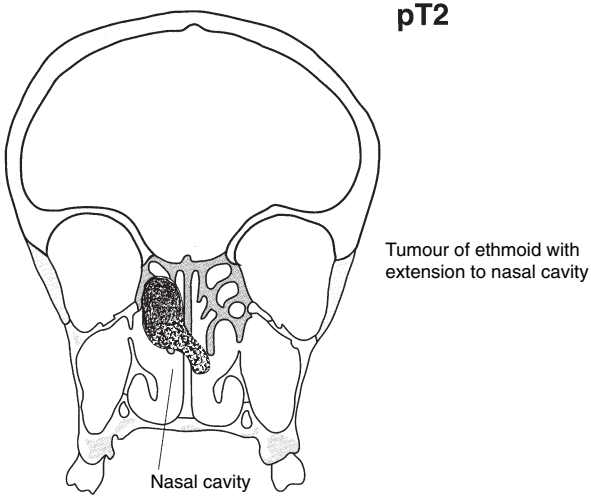


FIGURE 13.6. Ethmoid sinus carcinoma.

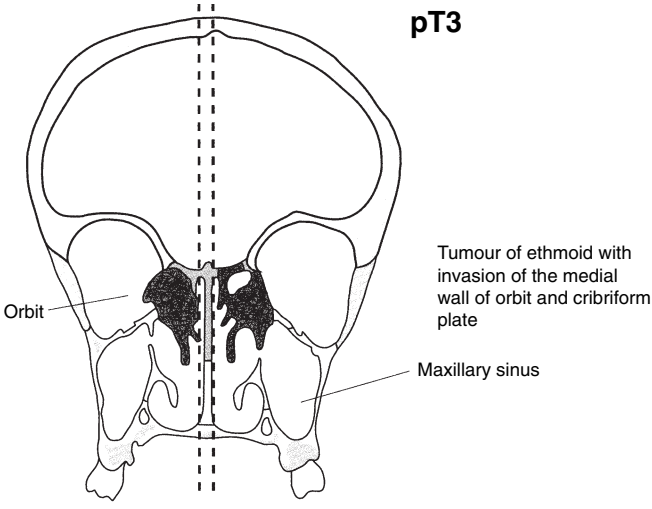


FIGURE 13.7. Ethmoid sinus carcinoma.

pT3 tumour extends to medial wall or floor of orbit, maxillary sinus, palate, or cribriform plate
pT4 tumour invades any of:
4a: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
4b: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx, clivus.

Invasion of bone includes only involvement of the spongiosa, not the cortex.
Presentation is not infrequently late with bone destruction already present.

5. LYMPHOVASCULAR INVASION
Present/absent.
Intra-/extratumoral.

6. LYMPH NODES
Site/number/size/number involved/limit node/extracapsular spread.
Regional nodes: cervical.

Level I: submental, submandibular
Level II: upper jugular
Level III: middle jugular
Level IV: lower jugular
Level V: posterior triangle.

A selective neck dissection will ordinarily include a minimum of six lymph nodes, a (modified) radical dissection 10 lymph nodes.

pN0 no regional lymph node metastasis
pN1 metastasis in a single ipsilateral node ≤ 3 cm
pN2 metastasis in
a. ipsilateral single node > 3 cm but ≤6 cm
b. ipsilateral multiple nodes ≤ 6 cm
c. bilateral, contralateral nodes ≤ 6 cm
pN3 metastasis in a lymph node > 6 cm.

7. EXCISION MARGINS
Distance (mm) to the nearest painted excision margin.
Due to anatomical limitations on resection, margins are usually only several millimetres.

8. OTHER PATHOLOGY
Malignant tumours are more common than benign in the paranasal sinuses with the reverse being the case in the nasal cavity. Equivalent nasal cavity tumours have a better prognosis. Markers are of use in differentiating carcinoma from malignant melanoma and lymphoma. Fifty-five percent of sinonasal malignancies occur in the maxillary sinus, 35% in the nasal cavity and 9% in the ethmoid sinus. The majority of lesions

(85%) are squamous cell carcinoma and its variants with adenocarcinoma representing only 5–10% of cases. About 10% of patients present with nodal metastases.

Prognosis
Prognosis is strongly related to tumour stage. Treatment is by a combination of surgery and radiotherapy, with 5-year survival about 60%. Undifferentiated carcinoma has a very poor prognosis and histologically squamous and glandular differentiation are precluded by definition. Undifferentiated carcinoma of nasopharyngeal type is radiosensitive with remission in 80% and 10-year survival in 40%.

9. OTHER MALIGNANCY

Lymphoma
— diffuse large B-cell lymphoma is commonest; CD20 positive.
— angiocentric T-cell lymphoma [sinonasal NK (natural killer)/T cell lymphoma]: destructive nasal/midline tumour with large areas of zonal necrosis and vasculocentric/destructive. It comprises polymorphic tumour cells (CD56 positive/CD3±) which may be hard to recognize amongst the inflammatory infiltrate. EBV associated and of poor prognosis. Serum ANCA levels help to distinguish it from Wegener's granulomatosis—another cause of sinonasal lethal midline granuloma.

Plasmacytoma/myeloma
— development of myeloma may take a number of years.
— κ, λ light chain restriction and clinical evidence of myeloma, e.g. elevated erythrocyte sedimentation rate (ESR), serum immune paresis, and monoclonal gammopathy, Bence–Jones proteinuria, radiological lytic bone lesions.

Rhabdomyosarcoma (embryonal—children), angiosarcoma, fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, osteosarcoma, odontogenic tumours by direct spread.

Olfactory neuroblastoma, primitive neuroectodermal tumour (PNET)
— olfactory neuroblastoma: small, round blue cell tumour aggregates (lobules/nests ± rosettes) in a fibrillary stroma with calcification. Tumours confined to the nasal cavity have a reasonable prognosis while those in the nasal cavity and paranasal sinuses an intermediate outlook. Extranasal/paranasal and visceral lesions are of poor prognosis. Treatment is by a combination of surgery and radiotherapy. Overall 5-year survival is 50–60% with a tendency for late recurrences. Variably positive neuron-specific enolase (NSE), neurofilament, chromogranin, cytokeratin, S100 and glial fibrillary acidic protein (GFAP)

Immunohistochemistry aids in distinction from the differential diagnoses of malignant melanoma, lymphoma, plasmacytoma and embryonal/alveolar rhabdomyosarcoma. The less differentiated PNET tumour is MIC 2 (CD99) positive and variably neuroendocrine marker positive (NSE, PGP 9.5, neurofilament) but potentially responsive to high-dose irradiation and multi-drug chemotherapy (75% 5-year survival). There is overlap with cytoteratin positive sinonasal neuroendocrine carcinoma.

Pituitary carcinoma

Chordoma

— locally destructive low-grade malignancy derived from notochordal remnants with characteristic vacuolated physaliphorous cells positive for S100, cytokeratins (CAM5.2, AE1/AE3, CK8, CK19), EMA and rarely CEA.

Malignant meningioma

Ewing's sarcoma, malignant teratoma

14
Laryngeal Carcinoma

1. GROSS DESCRIPTION

Specimen

— biopsy/hemi-/partial or total laryngectomy/neck dissection.
— size (cm) and weight (g).

Typically presenting with hoarseness, investigation is by indirect laryngoscopy with biopsy. Chest X-ray and endoscopy of the upper aerodigestive tract are done to exclude a concurrent cancer elsewhere. CT and MRI are used to stage the tumour and cervical lymph node enlargement necessitates FNA to establish if there are metastases. Tumour stage and fitness of the patient determine the appropriate choice of treatment, i.e. radiotherapy, laryngectomy, neck dissection. Laryngectomy may also accompany a pharyngectomy for cancer of the hypopharynx.

Tumour

Site

supraglottic	20%
glottic	70%
infraglottic	5%
transglottic	5%

Supraglottis: from the tip of the epiglottis to the true cords including the aryepiglottic folds, false vocal cords and ventricles.

Glottis: true cords and anterior commissure.

Subglottis: from the lower border of the true cords to the first tracheal cartilage.

Anterior/posterior/lateral(right, left)/commissural/ ventricles/false cords. Anterior glottis is the commonest site.

Size

— length × width × depth (cm) or maximum dimension (cm).

Appearance

— polypoid/verrucous/plaque/ulcerated/multifocal.

Edge
— circumscribed/irregular.

2. HISTOLOGICAL TYPE

Squamous cell carcinoma
— 90% of cases.
— keratinizing/non-keratinizing.

variants:

— verrucous: broad based exophytic and "church-spire" hyperkeratosis with a pushing deep margin of cytologically bland bulbous processes arising in the glottis. Locally invasive, rarely metastatic, radiation may result in anaplastic change. 70% 5-year survival.
— papillary: >70% papillary or exophytic fronds, covered by malignant type epithelium with focal invasion at the base. Better prognosis (70% 5-year survival).
— spindle cell: polypoid, glottic, elderly, ±history of irradiation for previous carcinoma. A minor squamous element is present (in-situ or invasive) with a major variably pleomorphic fibrosarcoma-like component. Diffuse or focal cytokeratin (70% – AE1/AE3) positivity suggests that it is a metaplastic form of carcinoma. Prognosis is better if polypoid and superficial than infiltrative, when the outlook is poor. Distinguish from sarcoma and bizarre post-irradiation granulation tissue.
— basaloid: poor prognosis, nests of basaloid cells with peripheral palisading and central comedonecrosis, hyalinised stroma.

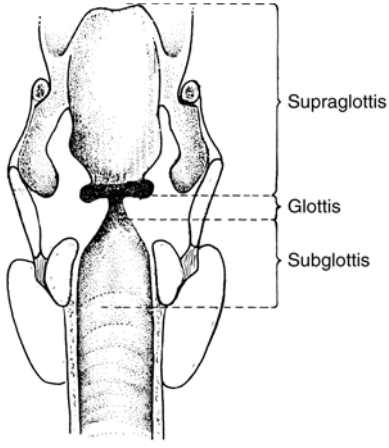


FIGURE 14.1. Larynx.

— adenoid squamous: usual prognosis, acantholytic (pseudoglandular) pattern.
— adenosquamous: poor prognosis, mixed differentiation squamous carcinoma and adenocarcinoma (either obvious glands or solid with mucin positive cells).

Undifferentiated carcinoma
— absence of squamous or glandular differentiation.
— includes lymphoepithelioma type.

Neuroendocrine carcinomas
— chromogranin/CD56/synaptophysin ± CAM5.2 positive.
— well differentiated: carcinoid tumour.
— moderately differentiated: atypical carcinoid tumour.
— poorly differentiated: small cell/large cell carcinoma.

Atypical carcinoid and large cell neuroendocrine carcinoma are commoner in the larynx than carcinoid tumour and are aggressive lesions with 50% mortality.

Adenocarcinoma
— salivary type, e.g. adenoid cystic, mucoepidermoid carcinomas of mucosal gland origin.
— adenocarcinoma of no specific type.

Metastatic carcinoma
— direct spread: thyroid, oesophagus.
— distant spread: malignant melanoma, kidney, breast, pancreas, colon, ovary, prostate.

3. DIFFERENTIATION
Well/moderate/poor/undifferentiated, or Grade 1/2/3/4.

— for squamous carcinoma based on cellular atypia, keratinization and intercellular bridges.
— undifferentiated carcinoma shows no squamous or glandular differentiation (grade 4).

4. EXTENT OF LOCAL TUMOUR SPREAD
Border: pushing/infiltrative.
Lymphocytic reaction: prominent/sparse.
A glottic tumour is best sliced horizontally to demonstrate its anatomical relationships, a supraglottic tumour sagitally.

Anterior
— mucous membrane, cricothyroid membrane, thyroid cartilage, thyroid gland, strap muscles, jugular vein.

Superior
— base of epiglottis, vestibular folds, pyriform fossa and limits.

Inferior
— trachea and limit.

The TNM classification applies only to carcinomas.

pTis carcinoma in situ.

Supraglottis
pT1 one subsite, normal mobility
pT2 mucosa of more than one adjacent subsite of supraglottis or glottis or adjacent region outside the supraglottis; without fixation
pT3 cord fixation or invades post cricoid area, pre-epiglottic tissues, paraglottic space, thyroid cartilage erosion
pT4a through thyroid cartilage and/or into trachea, soft tissues of neck: deep/extrinsic muscle of tongue, strap muscles, thyroid, oesophagus
pT4b prevertebral space, mediastinal structures, carotid artery.

Glottis
pT1 limited to vocal cord (s), normal mobility
(a) one cord
(b) both cords
pT2 into supraglottis and/or subglottis and/or impaired cord mobility
pT3 cord fixation and/or into paraglottic space and/or thyroid cartilage erosion
pT4a through thyroid cartilage or into trachea, soft tissues of neck: deep/extrinsic muscle of tongue, strap muscles, thyroid, oesophagus
pT4b prevertebral space, mediastinal structures, carotid artery.

Subglottis
pT1 limited to subglottis
pT2 extends to vocal cord(s) with normal/impaired mobility
pT3 cord fixation
pT4a through cricoid or thyroid cartilage and/or into trachea, deep/extrinsic muscle of tongue, strap muscles, thyroid, oesophagus
pT4b prevertebral space, mediastinal structures, carotid artery.

5. LYMPHOVASCULAR INVASION
Present/absent.
Intra-/extratumoral.

6. LYMPH NODES
The incidence of nodal metastases at presentation varies according to the site of the primary tumour from glottic (<10%) to supra-/infraglottic (30–50%). Well-differentiated carcinomas are less likely to metastasize than poorly differentiated cancers.
Site/number/size/number involved/limit node/extracapsular spread.
Regional nodes: cervical.

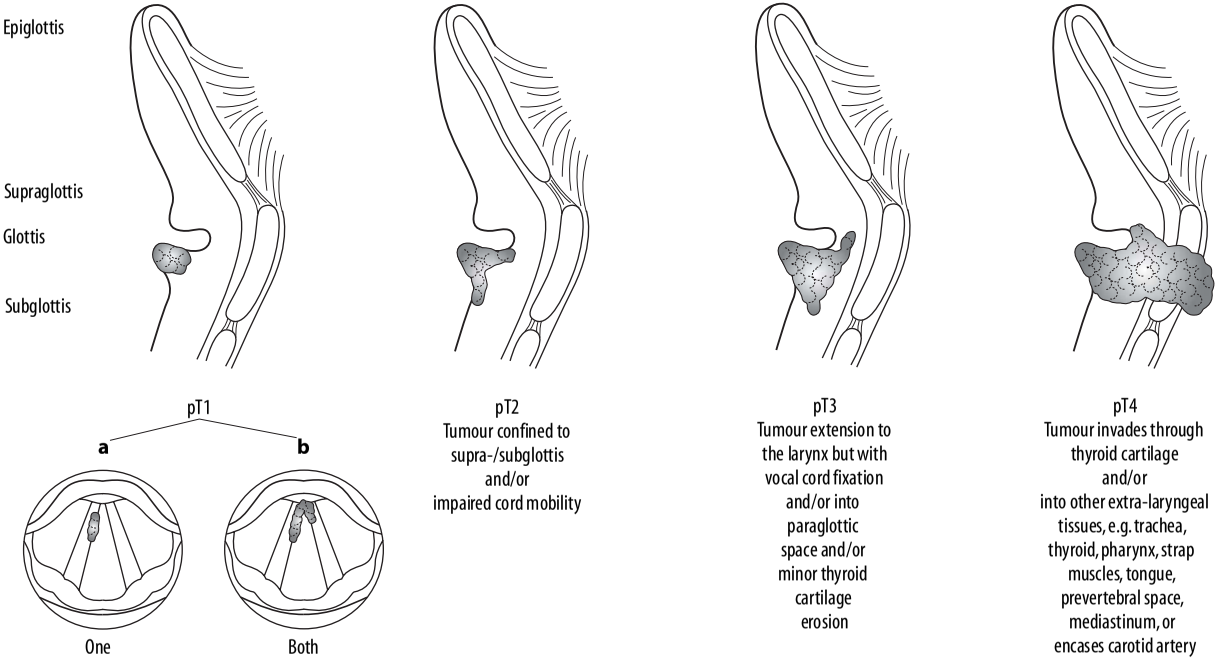


FIGURE 14.2. Laryngeal carcinoma: glottic.

Level I: submental, submandibular
Level II: upper jugular
Level III: middle jugular
Level IV: lower jugular
Level V: posterior triangle

A selective neck dissection will ordinarily include a minimum of six lymph nodes, a (modified) radical dissection 10 lymph nodes.

pN0 no regional lymph node metastasis
pN1 metastasis in single ipsilateral node ≤ 3 cm
pN2 metastasis in:
a. single ipsilateral node > 3 cm but ≤6 cm
b. ipsilateral multiple nodes ≤ 6 cm
c. bilateral, contralateral nodes ≤ 6 cm
pN3 metastasis in lymph node > 6 cm.

7. EXCISION MARGINS

Distances (mm) to the tracheal limit, aryepiglottic fold and pre-laryngeal anterior fascia of infiltrating carcinoma and any mucosal dysplasia or carcinoma in situ.

8. OTHER PATHOLOGY

Laryngeal carcinoma is predominantly (>95%) in males who smoke and are 50–60 years of age. Smokers and heavy voice users can develop keratosis with hoarseness and thickened white cords on laryngoscopy. A proportion may be associated with dysplasia and progression to carcinoma in situ and eventually over a period of years squamous carcinoma. These premalignant changes can be treated by local excision, laser or irradiation. Carcinoma in situ may be leukoplakic, erythroplakic or inapparent and biopsy is necessary.

Radionecrosis

— post-radiotherapy confluent necrosis which may lead to local airway obstruction and necessitate laryngectomy.

Concurrent carcinoma bronchus/oropharynx

— 10–15%.

Verrucous squamous cell carcinoma has to be distinguished from benign squamous epithelial papilloma and hyperplasia by its pushing deep margin. It can also co-exist with squamous carcinoma of usual type. Beware granular cell tumour with overlying pseudoepitheliomatous hyperplasia—the granular cells (Schwann cell origin) are S100 protein positive.

Juvenile laryngeal papillomatosis (multiple squamous papillomas of the upper respiratory tract) is a rare cause of squamous cell carcinoma, usually after radiotherapy.

Prognosis
Prognosis relates to tumour site, stage and histological grade. Early (pT1, pT2) glottic and supraglottic carcinoma may be treated by local excision, laser or radiotherapy. Partial laryngectomy (supraglottic or vertical hemilaryngectomy) may be carried out for small volume T2 or T3 cancers. Advanced carcinoma, infraglottic and transglottic tumours and cancers refractory to radiotherapy usually necessitate laryngectomy supplemented by radiotherapy.
Site-related 5-year survival:

glottic	80%
supraglottic	65%
transglottic	50%
subglottic	40%.

Stage-related 5-year survival:

glottic	I	90%
	II	85%
	III	60%
	IV	<5%.

Most glottic carcinomas are well to moderately differentiated, while non-glottic carcinomas are more frequently moderately to poorly differentiated.

9. OTHER MALIGNANCY

Lymphoma/leukaemia
— primary MALToma or secondary to nodal/systemic disease.
— sinonasal (angiocentric) T/NK cell lymphoma.

Plasmacytoma/myeloma
— initially localized but generally becomes part of disseminated myeloma. Look for κ, λ light chain restriction and evidence of systemic disease (elevated ESR, serum immune paresis and monoclonal gammopathy, Bence–Jones proteinuria, radiological lytic bone lesions).

Sarcoma, particularly low-grade chondrosarcoma and rhabdomyosarcoma (embryonal—childhood), occasionally angiosarcoma, liposarcoma, fibrosarcoma

Malignant melanoma
— primary or secondary (commoner). S100, HMB-45, melan-A positive.

Kaposi's sarcoma
— AIDS.

15
Salivary Gland Tumours

1. GROSS DESCRIPTION

Specimen

— parotid/submandibular/sublingual/minor (oral).
— conservative superficial/radical parotidectomy, submandibulectomy, excision of oral tumour (sublingual glands, or minor salivary glands of mucosal origin), neck dissection.
— size (cm) and weight (g).
— salivary gland tumours present as persistent unilateral enlargement the majority of which are in the parotid gland and are benign. There is a higher incidence of carcinoma arising in the submandibular glands, sublingual and minor glands of the oral cavity. Investigation is plain X-ray (for calculus), ultrasound scan (for cystic lesions), CT and MRI scan (for tumour stage). FNA is the method of choice in obtaining a likely tissue diagnosis for the purposes of planning operative management. Surgical treatment is by partial or total excision of the gland to include the tumour mass with a surround of either salivary gland tissue or soft tissues. Parotid tumours may also require excision of the skin and soft tissues of the side of the face and upper neck.

Tumour

Site

— salivary gland/nodal.
— parotid gland: superficial or deep lobe (subdivided by the plane of the facial nerve). Most arise in the superficial lobe.
— bilateral: Warthin's tumour, pleomorphic adenoma, acinic cell carcinoma.

Size

— length × width × depth (cm) or maximum dimension (cm).

Appearance

— solid/cystic.
— mucoid/chondroid/necrotic/fleshy/scirrhous.

Edge
— circumscribed/irregular: presence of macroscopic extraglandular extension.

Gland
— intra-salivary lymph nodes/nerves.

2. HISTOLOGICAL TYPE

Adenomas
— pleomorphic; 70% of salivary gland tumours, 80% in the parotid.
— myoepithelioma.
— basal cell.
— Warthin's tumour (adenolymphoma).
— oncocytoma.
— canalicular.
— sebaceous.
— ductal papilloma (inverted/intra-ductal/sialadenoma papilliferum).
— cystadenoma (papillary/mucinous).

Carcinomas
— acinic cell.
— mucoepidermoid: low-grade/well differentiated, high-grade/poorly differentiated.
— adenoid cystic: cribriform/tubular/solid.
— polymorphous low-grade.
— epithelial/myoepithelial.
— salivary duct.
— basal cell.
— sebaceous.
— oncocytic.
— papillary cystadenocarcinoma.
— mucinous (colloid).
— adenocarcinoma, not otherwise specified (NOS).
— squamous.
— carcinoma in pleomorphic adenoma (ex-PSA) usually adenocarcinoma, no special type.
— myoepithelial: spindle/clear cell types.
— lymphoepithelial.
— small cell.
— undifferentiated.
— carcinosarcoma.

Lymphoma
— extranodal lymphoma of salivary gland (MALToma).
— lymphoma of salivary gland nodes (nodal lymphoma).

Metastatic carcinoma
— squamous cell carcinoma of head and neck region and upper aerodigestive tract, malignant melanoma from scalp or facial skin, renal cell

carcinoma, lung and breast carcinoma, prostate, large bowel carcinomas. The metastasis is to adjacent or intrasalivary lymph nodes and the enlargement mimics a primary lesion. Note that secondary carcinoma of the submaxillary region is commoner than a primary neoplasm.

3. DIFFERENTIATION

Well/moderate/poor/undifferentiated, or Grade1/2/3/4.

— grade is type dependent, e.g. acinic cell, basal cell and polymorphous low-grade adenocarcinomas are low grade but salivary duct, primary squamous cell and undifferentiated carcinomas are high grade. Adenocarcinoma, NOS is graded according to the percentage tumour gland formation, and adenoid cystic carcinoma is grade 2 (intermediate) unless it is solid pattern (grade 3, high grade). Mucoepidermoid carcinoma is assessed on the degree of cystic change, atypia, necrosis, perineural invasion and mitoses as low, intermediate or high grade. The latter tend to be solid and epidermoid in type with a scanty mucous component.
— a majority of salivary gland tumours are low grade but elderly patients not infrequently present with high-grade tumours.

4. EXTENT OF LOCAL TUMOUR SPREAD

Border: pushing/infiltrative.

— infiltrative margins are a useful diagnostic feature of malignancy in low-grade lesions, e.g. polymorphous low-grade adenocarcinoma and adenoid cystic carcinoma.

Lymphocytic reaction: prominent/sparse.
Perineural space involvement particularly adenoid cystic carcinoma resulting in intractable facial pain.
Skin, subcutis.

The TNM classification applies to major salivary glands: parotid, submandibular and sublingual. Minor salivary gland tumours (i.e. from the mucosa of the upper aerodigestive tract) are classified according to anatomical site, e.g. lip.

pT1 tumour ≤2 cm, without extraparenchymal extension*
pT2 tumour >2 to 4 cm, without extraparenchymal extension*
pT3 tumour with extraparenchymal extension, and/or >4 cm
pT4 tumour invades
a. skin, mandible, ear canal, and/or facial nerve
b. base of skull, and/or pterygoid plates and/or encases carotid artery.

5. LYMPHOVASCULAR INVASION

Present/absent.
Intra-/extratumoral.

*Extraparenchymal extension is clinical or macroscopic evidence of invasion of skin, soft tissues, bone or nerve; microscopic evidence alone is not sufficient.

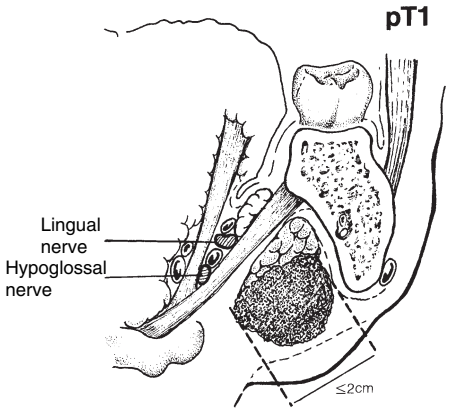


FIGURE 15.1. Salivary gland carcinoma.

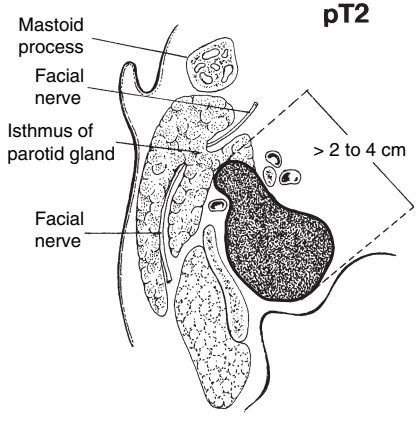


FIGURE 15.2. Salivary gland carcinoma.

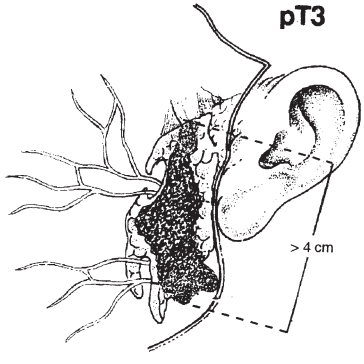


FIGURE 15.3. Salivary gland carcinoma.

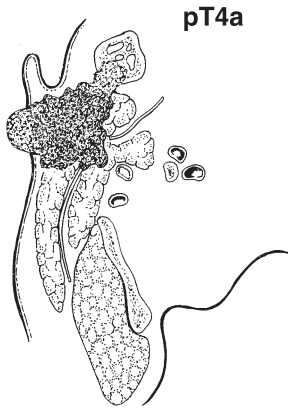


FIGURE 15.4. Salivary gland carcinoma.

6. LYMPH NODES

Intra-/extraglandular: the parotid gland can contain up to 20–30 intraglandular lymph nodes.
Site/number/size/number involved/limit node/extracapsular spread.
Regional nodes: cervical.

Level I:	submental, submandibular
Level II:	upper jugular
Level III:	middle jugular
Level IV :	lower jugular
Level V:	posterior triangle.

A selective neck dissection will ordinarily include a minimum of six lymph nodes, a (modified) radical dissection 10 lymph nodes.

pN0	no regional lymph node metastasis
pN1	metastasis in single ipsilateral node ≤3 cm
pN2	metastasis in:
	a. single ipsilateral node >3 cm but ≤6 cm
	b. ipsilateral multiple nodes ≤6 cm
	c. bilateral or contralateral nodes ≤6 cm
pN3	metastasis in lymph node >6 cm.

Regional nodes are the commonest site of metastasis followed by lungs and bone.

7. EXCISION MARGINS

Distance (mm) to the nearest painted excision margin.
Pleomorphic adenomas should not be surgically enucleated as the irregular margin can lead to residual tumour and local recurrence.

8. OTHER PATHOLOGY

Fine needle aspiration cytology has an important role to play in the primary diagnosis of salivary gland enlargement and is capable of designating benignity and malignancy in a majority of cases. It can indicate non-neoplastic disorders such as simple cysts, abscess and fatty infiltration. The separation of benign from malignant salivary tumours results in more appropriate surgery (superficial conservative vs. radical parotidectomy) or the avoidance of it (lymphoma, secondary carcinoma). The experienced cytopathologist can in many cases obtain sufficient material to stipulate the tumour subtype. Some pitfalls are cystic lesions (simple cyst vs. cystic salivary tumour, e.g. mucoepidermoid carcinoma, acinic cell carcinoma or metastatic squamous carcinoma), clear cell lesions (primary epithelial or myoepithelial tumour vs. secondary renal, lung or thyroid carcinoma), metastases (primary squamous or mucoepidermoid carcinoma vs. secondary squamous carcinoma), the onset of low-grade lymphoma in lympho(myo-)epithelial sialadenitis and distinction from extranodal lymphoma and chronic sialadenitis. The technique is obviously reliant on representative sampling of the tumour and there can be a degree of cytological overlap between subtypes, e.g. pleomorphic adenoma, adenoid cystic carcinoma and polymorphous low-grade adenocarcinoma.

Necrotizing sialometaplasia of minor salivary glands in the mouth and palate can mimic carcinoma, e.g. mucoepidermoid carcinoma. It presents as an ulcerating lesion in middle-aged men.

There is a higher incidence of carcinoma in minor salivary glands (e.g. polymorphous low-grade adenocarcinoma of the palate or floor of mouth): palate 44%, submaxillary glands 38%, parotid 17% of salivary carcinomas.

Salivary tumours with clear cells tend to be malignant, and must also be distinguished from secondary renal cell carcinoma. A wide range of salivary tumours can show clear cell differentiation: acinic cell, mucoepidermoid, epithelial-myoepithelial, sebaceous, clear cell carcinomas and malignant myoepithelioma. Abdominal investigation may be necessary to distinguish metastatic renal cell carcinoma (vascular stroma, glycogen/fat-rich cells), S100, melan-A and HMB-45 (clear cell melanoma), and thyroglobulin/TTF-1 (clear cell thyroid carcinoma). Primary clear cell carcinoma of low grade arises in minor salivary glands, has uniform clear cells in a dense hyalinizing stroma and is locally infiltrative.

Acinic cell carcinomas occur in the parotid gland and have deceptively bland granular cells with a variably solid, papillary, clear cell, follicular or microcystic pattern but can still infiltrate and metastasize and more aggressive pleomorphic variants occur. Overall recurrence can be seen in 10–30% and death in about 6%. Peak incidence is in the third decade of life but, like mucoepidermoid carcinoma, acinic cell carcinomas are seen in childhood and teenage years. Gross invasion, cellular pleomorphism and incomplete primary excision are adverse indicators.

Mucoepidermoid carcinoma affects palate and parotid gland and is the commonest malignant salivary gland tumour (30% of cases). It shows a spectrum of epidermoid and mucous cells in varying proportions (mucin stains may be necessary). Well-differentiated lesions may be largely cystic with only mural tumour. Poorly differentiated (high-grade) lesions are more solid, squamoid and infiltrative. The mucin and keratin can be extruded into the interstitium causing an inflammatory reaction. Tumour grade dictates prognosis with multiple local recurrences dominating and nodal metastases late.

Adenoid cystic carcinoma forms 5% of salivary gland neoplasms but 20% of the carcinomas with equal distribution between the parotid and minor glands (palate). It shows biphasic cell differentiation (epithelial/myoepithelial: cytokeratin/S100, CK5/6 and smooth muscle actin positive) and biphasic histochemical staining of PAS positive luminal mucus and alcian blue positive matrix. It typically shows cribriform, hyaline and tubular patterns and indolent perineural spread with facial pain and late lymph node involvement. It is slow growing but highly malignant and locally recurrent. Prognosis relates adversely to a solid (basaloid) growth pattern, stage and incomplete primary excision, with radical surgery being the treatment of choice. Margins can be difficult to define, as there is often spread beyond the identifiable clinical edge.

Polymorphous low-grade adenocarcinoma is characterized by cellular uniformity and architectural diversity (solid/cribriform/single cell/cords/tubular/ductal/papillary) with abundant stroma. Typically in the palate (second commonest after adenoid cystic carcinoma) with local recurrence in 21%, nodal metastases in 6.5% and distant metastases in 1.8%. An infiltrative margin and perineural invasion can be helpful in making the diagnosis. A somewhat more aggressive tumour is the related low-grade papillary adenocarcinoma.

Epithelial/myoepithelial carcinoma is a low-grade malignancy mainly of the parotid gland and recurs in one-third of cases, comprising ductal cells and outer clear myoepithelial cells in a biphasic pattern. Myoepithelial differentiation can be demonstrated by cytokeratin 5/6, S100 and smooth muscle actin. Although circumscribed, it has an infiltrative margin with perineural invasion. Death can occur in 7% and nuclear atypia in >20% of cells is an adverse prognostic factor. Occasionally one element dedifferentiates resulting in carcinomatous or sarcomatous overgrowth.

Myoepithelial carcinoma is a spindle cell lesion with mitotic activity, nuclear atypia, necrosis and invasion.

Ductal carcinoma resembles high-grade ductal carcinoma in situ of the breast. It shows aggressive behaviour with poor prognosis and 70% die within 3 years. Patients are >50 years of age and the male to female ratio is 3:1 with parotid being the main site. A low-grade variant also exists.

Primary squamous cell carcinomas (5–10%) occur mostly in the parotid gland and are aggressive with 5-year survival rates of 40%. Metastases to

the parotid gland from other sites must be excluded, commonly upper aerodigestive tract or skin. Some primary lesions represent mucoepidermoid carcinoma or carcinoma within a mixed tumour.

Carcinoma in pleomorphic adenoma (3–4% of cases) is unusual and manifests itself as regrowth or facial pain in an existing lesion present for 15–30 years (9.5% risk after 15 years). In descending order of frequency the malignancy is carcinoma (adenocarcinoma of no specific type, poorly differentiated ductal and undifferentiated), malignant myoepithelioma, carcinosarcoma and metastasizing pleomorphic adenoma. Prognosis which is adverse relates strongly to the degree of extension of the malignancy beyond the capsule of the original benign tumour.

Basal cell carcinoma is the malignant counterpart of basal cell adenoma (solid nests surrounded by basal hyaline lamina material) except that it shows infiltration, perineural and vascular invasion. It occurs in the patient's parotid gland, 50–60 years of age.

Carcinosarcoma, small cell carcinoma and undifferentiated carcinoma (some of which are lymphoepitheliomatous in character and EBV related similar to nasopharyngeal carcinoma) have poor prognosis.

Most low-grade carcinomas of mucoepidermoid or acinic cell type can be treated by superficial parotidectomy, whereas more radical surgery with sacrifice of the facial nerve is needed for large (>4 cm), higher-grade or advanced carcinomas. Submandibular and sublingual tumours are treated by total removal of the gland with a margin of normal tissue.

Prognosis

Prognosis relates to tumour stage, anatomical location and histological type and grade.

— minor salivary gland tumours have a higher incidence of recurrence and metastases than equivalent parotid lesions.
— examples of 5-year survival rates: low-grade mucoepidermoid, 90–95%; high-grade mucoepidermoid, 50–60%; squamous cell carcinoma, 40%.
— histological type:

better prognosis:	low-grade mucoepidermoid/acinic cell carcinomas
worse prognosis:	high-grade mucoepidermoid/acinic cell carcinomas; adenoid cystic carcinoma, malignant mixed tumour, salivary duct carcinoma, squamous carcinoma.

9. OTHER MALIGNANCY

Rhabdomyosarcoma

— children. Desmin/myo D1/myogenin positive. Note that mucoepidermoid and acinic cell carcinomas can also typically occur in childhood and young adults.

Malignant fibrous histiocytoma, fibrosarcoma, malignant peripheral nerve sheath tumour
— adults.

Lymphoma
— 2–5% of salivary gland neoplasms.
— 20% have Sjögren's syndrome or LESA (lymphoepithelial or myoepithelial sialadenitis).
— one-third are diffuse large B-cell lymphoma, of nodal or parenchymal origin.
— one-third are follicular lymphoma, usually of nodal origin.
— one-third are MALToma. LESA has a ×40 increased risk of developing low-grade lymphoma and 15–20% do so over a variable period of 5–20 years. MALToma is characterized by lymphoepithelial lesions surrounded by broad haloes or sheets of centrocyte-like (marginal zone/monocytoid) B cells. Other features include monotypic plasma cells and follicular colonization. High-grade transformation to large cell lymphoma can occur. Polymerase chain reaction demonstration of clonality does not always reliably predict those lymphoid lesions that will progress to clinical lymphoma.

16

Thyroid Gland Tumours (with comments on parathyroid)

1. GROSS DESCRIPTION

Specimen

— fine needle aspirate/partial or (sub)total thyroidectomy/left or right lobectomy/isthmusectomy/parathyroidectomy/selective neck dissection.
— size (cm) and weight (g).
— thyroid gland tumours usually present with enlargement due to a solitary "cold" nodule with euthyroid function. Differentiated (papillary, follicular) cancer may present with cervical lymph node or sclerotic bone metastases. Undifferentiated cancers are often of rapid onset with symptoms due to infiltration or compression of local structures, e.g. hoarseness, dysphagia or respiratory stridor. FNA is the investigation of choice, either of a clinically palpable lesion or under ultrasound guidance with follow-up for benign cytology and surgery for a suspicious or malignant aspirate. Core needle biopsy may be used to distinguish between anaplastic carcinoma and malignant lymphoma. The extent of operative resection depends on the patient's age, gender, tumour type and stage.

Tumour

Site
— left/right lobe, isthmus, multifocal.

Size
— length × width × depth (cm) or maximum dimension (cm).

Appearance
— solid/cystic/calcified/haemorrhagic/pale/tan/ papillary.

Edge
— circumscribed/irregular (encapsulated/non-encapsulated).

Gland
— uniform, nodular, atrophic, pale in colour.

2. HISTOLOGICAL TYPE

Follicular adenoma

— usual type: macrofollicular; microfollicular; embryonal/fetal.
— variants: hyalinizing trabecular (HTA); oxyphil (Hürthle). Most HTAs (organoid trabecular/nested pattern of spindle cells and collagen) are benign but a minority show overlap features with papillary carcinoma and/or capsular/vascular invasion and are regarded as hyalinizing trabecular carcinoma. Thyroglobulin and NSE positive ± CK19.

Papillary carcinoma

— usual type: psammomatous.
— variants with worse prognosis:
diffuse sclerosing.
tall cell.
columnar cell.
solid.
trabecular.
diffuse follicular.
— variants with better prognosis:
encapsulated.
papillary microcarcinoma (≤1 cm).
— variants with usual prognosis:
follicular/oxyphil (Hürthle).

Follicular carcinoma

— widely invasive:
grossly apparent invasion of thyroid and/or soft tissue.
follicular/trabecular/solid patterns and vascular invasion.
cytological features of malignancy, e.g. atypia/mitoses/necrosis.
— minimally invasive:
encapsulated—angioinvasive with potential for metastases or capsular invasion with equivocal potential for metastases.
— variants: oxyphil (Hürthle)/clear cell.

Undifferentiated (anaplastic) carcinoma

— old age; 5–10% of cases. Rapid growth with involvement of vital neck structures and death in 6 months. Treatment (surgery, radiotherapy) is usually palliative.
— spindle/squamoid/giant cells ± cartilage/osseous metaplasia ± a differentiated component, i.e. evidence of origin from a more usual thyroid carcinoma, e.g. papillary carcinoma. Cytokeratin positive.

Poorly differentiated carcinoma

— "insular" carcinoma: large solid nests of small to medium sized round uniform tumour cells (medullary-like); thyroglobulin/TTF-1 positive,

calcitonin negative. Older age and grossly invasive with aggressive behaviour.
— also includes carcinomas of solid, scirrhous and trabecular patterns with necrosis and increased mitoses and/or of tall cell or columnar type either alone or as a dedifferentiated part of a carcinoma of more usual type, i.e. intermediate between differentiated (papillary/follicular) and undifferentiated (anaplastic) thyroid cancers.

Small cell carcinoma
— CD56/synaptophysin/CAM5.2 positive.

Medullary carcinoma
— 5–10% of cases, including mixed medullary/follicular.

Miscellaneous
— signet ring carcinoma, squamous carcinoma, mucoepidermoid carcinoma, carcinoma with thymus-like differentiation (CASTLE).

Metastatic carcinoma
— direct spread: upper aerodigestive tract, metastases in cervical lymph nodes.
— distant spread: malignant melanoma, breast, kidney, lung. Renal cell carcinoma can mimic primary clear cell (papillary or follicular) carcinoma of thyroid. Renal carcinoma may be multiple nodules, clear cells with glycogen and fat, a vascular stroma with haemorrhage and thyroglobulin/TTF-1 negative but positive for renal carcinoma markers (RCC antibody/vimentin/EMA/CD10).

3. DIFFERENTIATION
Well/moderate/poor/undifferentiated, or Grade1/2/3/4.
Traditional cytoarchitectural features may be used but grade is often determined by the nature of the tumour and its subtype, e.g. usual papillary carcinoma and minimally invasive follicular carcinoma are low grade, whereas undifferentiated carcinoma is high grade.

4. EXTENT OF LOCAL TUMOUR SPREAD
Border: pushing/infiltrative.
Lymphocytic reaction: prominent/sparse.
Perineural space involvement.
Solitary/multifocal, one or two lobes.
Involvement of lesion capsule, extracapsular spread.
Involvement of thyroid capsule, extrathyroid spread.
The TNM classification applies only to carcinomas.

pT1 tumour ≤ 2 cm in greatest dimension, limited to thyroid
pT2 2 cm < tumour ≤ 4 cm in greatest dimension, limited to thyroid
pT3 tumour >4 cm in greatest dimension, limited to thyroid or any tumour with minimal extrathyroid extension (e.g. to sternothyroid muscles or perithyroid tissues)

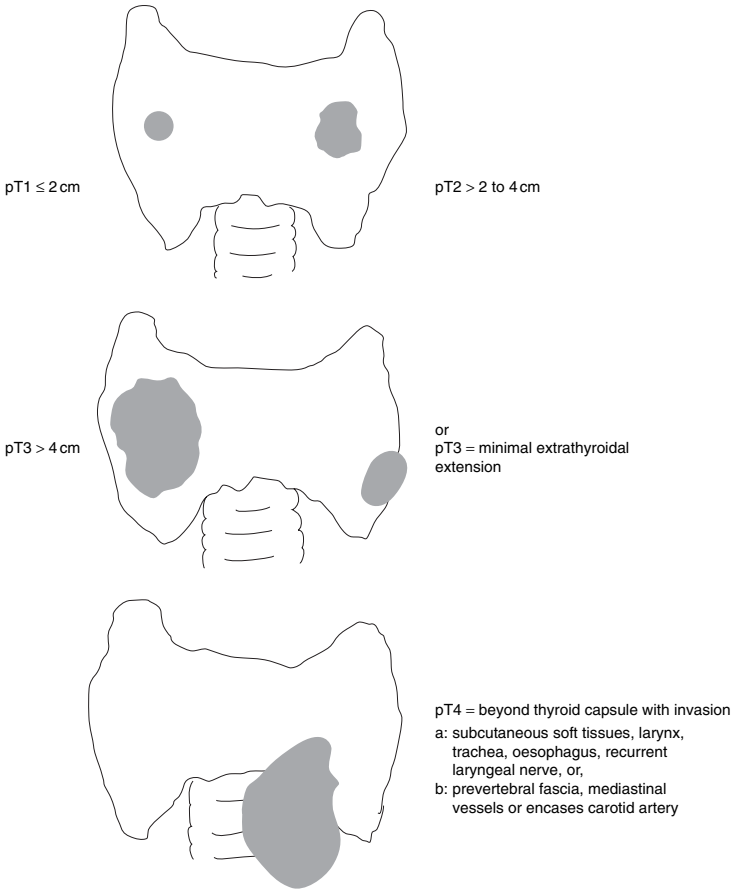


FIGURE 16.1. Thyroid carcinoma.

pT4 a. tumour extends beyond capsule and involves any of: subcutaneous soft tissues, larynx, trachea, oesophagus, recurrent laryngeal nerve
b. tumour invades prevertebral fascia, mediastinal vessels or encases carotid artery.

All anaplastic/undifferentiated thyroid carcinomas are pT4 (pT4a: intrathyroidal and considered surgically resectable; pT4b: extrathyroidal spread and considered surgically unresectable).

Other pathological descriptors:

— pT1, 2, 3: (i) grossly encapsulated tumour
(ii) grossly non-encapsulated tumour

— pT1a, b: (a) ≤1 cm, (b) 1 cm < tumour ≤ 2 cm
— pT3a, b: (a) >4 cm limited to thyroid, (b) minimal extrathyroid extension.

Separate clinical stage groupings are recommended for

1. Papillary or follicular carcinoma <45 years
2. Papillary or follicular carcinoma ≥45 years or medullary carcinoma, and,
3. Anaplastic/undifferentiated carcinoma (all stage IV).

Note that the Royal College of Pathologists currently recommend the 5th edition TNM classification.

5. LYMPHOVASCULAR INVASION

Present/absent.
Intra-/extratumoral.
Papillary carcinoma tends to lymphatic spread, follicular carcinoma to vascular spread.

6. LYMPH NODES

Site/number/size/number involved/limit node/extracapsular spread.
Regional nodes: cervical, upper/superior mediastinal

Level I: submental, submandibular
Level II: upper jugular
Level III: middle jugular
Level IV : lower jugular
Level V: posterior triangle.

A selective neck dissection will ordinarily include a minimum of six lymph nodes. Radical neck dissection is rarely performed for thyroid cancer.

pN0 no regional lymph nodes metastasis
pN1 metastasis in regional lymph node(s)
a. Level VI (including pre-/paratracheal and prelaryngeal nodes)
b. other unilateral, bilateral or contralateral cervical or upper/superior mediastinal nodes.

7. EXCISION MARGINS

Distances (mm) to the nearest painted capsule and surgical excision margins.

8. OTHER PATHOLOGY

Thyroid carcinoma is commoner in females (2.5:1) with the most frequent subtypes being differentiated papillary carcinoma (60%) and follicular carcinoma (20%). Previous irradiation predisposes to papillary carcinoma. *Papillary carcinoma* occurs in younger patients (average age 40 years), is multifocal (intraglandular lymphatic metastases) in a significant proportion of cases (20%) and shows a tendency to lymphatic

and lymph node spread (40–50%). Despite this, prognosis is excellent with a low disease-related mortality of about 5%. Papillary carcinoma may undergo cystic change with only residual mural tumour—a potential pitfall on FNA cytology. Invasion is not necessary for its diagnosis, which is mainly cytological. Diagnostic features are a combination of optically clear (orphan Annie) ground glass, overlapping nuclei with longitudinal grooves and nuclear pseudoinclusions. Stromal (not intrafollicular) and tumour cell-related psammoma bodies are present (50% of cases) and the stroma may be hyalinized, calcified or ossified. Architectural patterns are papillary, follicular or solid. The cells are thyroglobulin, TTF-1, cytokeratin 7, 19, galectin 3, HBME-1 and vimentin positive. Protooncogene product ret is variably positive. Notably the papillae of Grave's disease and nodular hyperplasia are CK19 focal or negative. Variants with an excellent prognosis are encapsulated carcinoma (totally surrounded by a capsule) and papillary microcarcinoma (<1 cm diameter: nodal metastases in 30%). Diffuse sclerosing (sclerosing, numerous psammoma bodies, solid foci, squamous metaplasia, heavy lymphocytic infiltrate), diffuse follicular, tall cell (older patients, papillary, oncocytic cell with height two to three times the width), columnar cell (nuclear stratification), solid and trabecular variants have significantly worse outlooks with a high risk of lymph node and distant metastases and disease-related mortality of up to 25%.

Follicular carcinoma tends to be in older patients than papillary carcinoma (50–60 years), unifocal and spreads via the blood stream to lung and bone. Minimally invasive carcinoma has an excellent prognosis with lymph node metastases in <5% of cases, whereas widely invasive tumour has a mortality of 30–35%. Multiple blocks (say 8–10) of the lesion and its capsule are required for the distinction between follicular adenoma and minimally invasive follicular carcinoma and diagnostic criteria are invasion of the capsule and/or its vessels. Cytological appearances of the epithelium are not helpful as adenomas may be markedly atypical, although solid, trabecular and microfollicular growth patterns can be a low-power clue. Carcinoma often has a thick, partly desmoplastic fibrous capsule and its full width must be traversed to qualify as invasion. The invasive tumour front may then form a second fibrotic interface with the parenchyma giving a dumbbell type of distribution. Vascular invasion, which is a more reliable indicator of malignancy, requires vessels to be:

a. within or outside the capsule, i.e. extratumoral,
b. of venous rather than capillary calibre with a definite muscular wall and endothelial lining, and
c. partially or completely plugged by tumour in the lumen with a definite point of attachment to the vessel wall. A cluster of follicular cells found free floating in a vascular lumen may represent artefactual detachment and is therefore discounted. CD31 immunostain helps to identify true vascular structures.

Note that capsular invasion needs to be distinguished from rupture following FNA cytology, which often shows organizing haemorrhage and a

reparative response. It can also cause tumour infarction and entrapment of cells within the capsule. Ultrasound and isotope scan examinations are combined with FNA cytology in the investigation of a wide range of thyroid enlargement. Cytology can be diagnostic in:

— inflammatory/autoimmune goitres:
  Hashimoto's thyroiditis (lymphocytes, Askanazy epithelial cells, colloid poor)
  de Quervain's thyroiditis (lymphocytes, giant cells, degenerate follicular cells)
  Riedel's struma (spindle cells, scant aspirate)
  abscess (polymorph rich).
— simple goitre: multinodular colloid/adenomatous (characteristically colloid rich/cell poor) and forming the vast majority of thyroid nodules.
— simple thyroid cyst: watery colloid and macrophages, scanty follicular cells.
— solitary, solid thyroid nodule: adenoma, follicular carcinoma, papillary carcinoma and medullary carcinoma (see above and below).

Adenoma and minimally invasive follicular carcinoma cannot be distinguished on FNA cytology. They are designated follicular lesion or neoplasm and are recognized by a variable cell rich/colloid poor pattern usually distinguishing them from simple goitres. Surgical excision is necessary for the histological assessment of capsular and vascular invasion.

— malignant goitre:
  widely invasive follicular carcinoma (cytological features of malignancy)
  malignant lymphoma (dispersed atypical lymphoid cells, lymphoglandular bodies)
  anaplastic carcinoma (spindle/giant cells with atypia).
— metastatic carcinoma:
  care must be taken to correlate imaging and FNA results closely as well as in assessing specimen adequacy sufficient to constitute a safe diagnosis, e.g. 5–10 groups of follicular cells with 10–20 cells per group. Diagnostic categories (thy1–5) are: insufficient, benign (nodular goitre, hyperplastic nodule, thyroiditis), follicular lesion, suspicious of malignancy and malignant (papillary carcinoma, anaplastic carcinoma, etc).

A higher proportion of Hürthle cell neoplasms are malignant than follicular neoplasms of usual type. Once again, capsular and vascular invasion are the hallmarks of malignancy. Hürthle cell carcinomas are aggressive with 5-year mortality rates of 20–40%. Follicular carcinomas are thyroglobulin, cytokeratin, TTF-1, EMA, galectin 3 and vimentin positive.

Medullary carcinoma (C-cell differentiation—5% of thyroid cancers) is in the majority of cases (80%) sporadic and unifocal. The hereditary forms occur in younger patients, can be multifocal and bilateral, associated with diffuse C-cell hyperplasia (>50 C cells per low power field), C-cell tumourlets and the MEN syndromes types II and III. Its morphology is het-

erogeneous, but usually comprises polygonal or plump spindle cells with a nested, trabecular or solid pattern. The hyalinized stroma can be calcified and is typically positive for amyloid and the cells are CEA, calcitonin and chromogranin/synaptophysin positive. Staining for TTF-1 and thyroglobulin is variable. Lymph node metastases are seen in 30–60% of cases but 5-year survival is 80%. High serum calcitonin levels, soft tissue and regional node involvement are associated with an adverse prognosis. Family members should be genetically screened (ret mutation) to establish the hereditary cases (autosomal dominant) and prophylactic thyroidectomy can be offered to affected children. Serial blocking of the gland is often required to look for C-cell hyperplasia and medullary microcarcinoma (≤1 cm). Treatment is surgical with radio-/chemotherapy of limited use.

Poorly differentiated carcinoma (70% 5-year survival) has a prognosis intermediate between that of usual thyroid carcinoma (90–95% 5-year survival) and anaplastic carcinoma. It is more frequently associated with old age, lymph node metastases and extrathyroid extension.

Anaplastic (syn. undifferentiated or sarcomatoid) carcinoma requires immunohistochemistry to distinguish it from high-grade lymphoma, malignant melanoma and angiosarcoma:

Immunophenotype

carcinoma	low molecular weight cytokeratin positive, thyroglobulin, CK19, TTF-1
lymphoma	CD45, CD20 (B) , CD3 (T)
melanoma	S100, HMB-45, melan-A
angiosarcoma	CD31, CD34, factor VIII positive.

Prognosis

Prognosis is worse in:

— male patients.
— patients >45 years of age.
— large tumours: <1.5 cm, excellent; >3.5–5 cm, poor.
— multicentric tumours.
— unencapsulated tumours.
— widely invasive tumours with extrathyroid extension.

Low-grade malignancy

— minimally invasive follicular carcinoma.
— papillary carcinoma.

Intermediate-grade malignancy

— widely invasive follicular carcinoma.
— adverse papillary carcinoma variants.
— medullary carcinoma.
— poorly differentiated carcinoma.
— lymphoma.

High-grade malignancy

— undifferentiated carcinoma.
— angiosarcoma.

Thus patients with differentiated cancer can be managed based on risk stratification according to gender, age, stage and histology (GASH):

patient	low-risk	F <45 years
	high-risk	<16 years, M/F >45 years
tumour	low-risk	papillary/minimally invasive follicular cancer <1 cm
	high-risk	papillary/follicular carcinoma >1 cm, multifocal or metastatic cancer.

Most solitary thyroid neoplasms are treated by lobectomy with isthmusectomy, or subtotal thyroidectomy if a firm preoperative diagnosis of malignancy has been made. Total or completion thyroidectomy tends to be reserved for worse prognosis subtypes of papillary carcinoma, widely invasive follicular carcinoma, medullary carcinoma (particularly if familial) and undifferentiated carcinoma (if operable). Extensive differentiated thyroid cancer may also require laryngectomy and pharyngectomy, and neck dissection is performed for clinically palpable nodal metastases. Other treatment modalities are tumour suppression by administration of thyroxine or radioactive iodine (papillary and follicular carcinoma) and radiotherapy (incompletely excised carcinomas or undifferentiated carcinoma). Treatment is therefore tailored to the patient's age, tumour type and stage.

9. OTHER MALIGNANCY

Lymphoma

— lymphocytic/Hashimoto's thyroiditis/MALToma.
— low grade: centrocyte-like cells, lymphoepithelial lesions, follicle loss/destruction.
— high grade: blast cells.

The majority of lesions are diffuse large B cell and there is some evidence for progression from Hashimoto's thyroiditis through low-grade to high-grade MALToma. Clinical onset can be rapid with compression of neck structures.

Overall 5-year survival is 50–80% and spread can occur to other MALT sites, e.g. gut. Advanced age, size (>10 cm), high grade and stage of disease (particularly perithyroidal soft tissue extension) can worsen 5-year survival rates to 40%.

Primary Hodgkin's disease is extremely rare.

Plasmacytoma

— as part of systemic myeloma: elevated ESR, serum immune paresis and monoclonal gammopathy, Bence–Jones proteinuria, radiological lytic bone lesions.

Angiosarcoma

— overlaps with undifferentiated carcinoma and is a pleomorphic tumour with vasoformative areas in elderly patients. Endothelial markers (CD31, CD34) are required for confirmation.

10. PARATHYROID

Hyperparathyroidism is due to oversecretion of parathormone and results in hypercalcaemia. It arises in three main contexts.

1. Primary hyperparathyroidism—oversecretion by one or more parathyroid glands sometimes due to diffuse hyperplasia(10–25% of cases, 25% of which are associated with MEN I and II syndromes) but more commonly (70–80% of cases) an adenoma.
2. Secondary hyperparathyroidism—as a physiological response of all four glands to chronic hypocalcaemia due to renal failure, malabsorption or vitamin D deficiency.
3. Tertiary hyperparathyroidism—autonomous hypersecretion in longstanding secondary hyperparathyroidism after correction of the hypercalcaemia.

Investigation is by serum calcium, phosphate and parathormone levels, and isotope scan with CT scan and MRI. Treatment is by removal of the adenoma (usually solitary, occasionally two) or hyperplastic glands, leaving a small amount (100 mg) of functioning tissue. Histologically there is overlap in the features of adenoma and nodular hyperplasia and designation is more appropriately decided by the number of enlarged glands (adenoma is usually solitary) and the clinical context. What is of crucial importance is that the pathologist confirms by frozen section to the surgeon that parathyroid tissue has been excised at neck exploration and not lymph node, thymic remnant or thyroid nodule. To this end each submitted specimen is finely weighed and its nature confirmed indicating whether there is any need for further surgical exploration.

Parathyroid carcinoma is rare (<2% of cases) and in elderly patients with high levels of parathormone. It may infiltrate adjacent soft tissues with difficulty in surgical excision. Histologically it has a solid or trabecular pattern with thick fibrous bands traversing it. Cytological atypia and mitoses are present but as these can be seen in an adenoma more reliable indicators are soft tissue, perineural and lymphovascular invasion. It may be resected in continuity with the ipsilateral lobe of thyroid gland, and neck dissection is considered for palpable metastases. Cervical and mediastinal lymph nodes, lungs, bone and liver are the commonest sites for metastatic spread.

Respiratory and Mediastinal Cancer

- Lung Carcinoma
- Malignant Mesothelioma
- Mediastinal Cancer

17
Lung Carcinoma

1. GROSS DESCRIPTION

Specimen

— exfoliative cytology/aspiration cytology or needle biopsy (percutaneous/transbronchial/CT guided)/bronchial biopsy/thoracoscopic biopsy/wedge resection/ sleeve resection/segmentectomy/(bi-)lobectomy/pneumonectomy (standard/extrapleural/extra-/intrapericardial) ± en bloc resection.
— resection can be either open or thoracoscopic (VATS: video-assisted thoracoscopic surgery).
— size (cm) and weight (g)/number of fragments.
— lung cancer may present due to ulceration (haemoptysis), obstructive effects (pneumonia), local infiltration (pleural effusion, chest wall pain/mass, hoarseness, Horner's syndrome due to apical Pancoast's tumour, superior vena cava syndrome), systemic effects (finger clubbing, paraneoplastic syndromes, weight loss) or as an incidental finding on radiology for other reasons. Investigation is by chest X-ray and staging by CT scan to assess spread to locoregional lymph nodes, liver, adrenal glands and brain. MRI can detect invasion into the vertebral column and spinal cord and CT/PET has a role in defining small (<1–2 cm) metastases. High resolution CT (HRCT) can demonstrate lymphangitis carcinomatosa. Tissue diagnosis is obtained in a high percentage (>90%) of cases by a variety and combination of techniques depending on the tumour site, local infiltration and type, viz, sputum cytology, bronchial brushings/washings/biopsy, transbronchial or image guided percutaneous FNA/needle core biopsy, open lung wedge or thoracoscopic biopsy. Thoracoscopic sampling of mediastinal lymph nodes is also used for staging purposes due to lack of sensitivity in CT scan assessment. In bronchogenic carcinoma diagnostic yield increases with the number of biopsy fragments, transthoracic FNA/needle biopsy being of particular use for peripheral lesions, and transbronchial biopsy for lymphangitis carcinomatosa and cancers causing bronchostenotic extrinsic compression. Where a preoperative diagnosis of a peripheral lesion has not been obtained intraoperative frozen section is indicated as a prequel to opting for either a more radical cancer resection operation or a lung sparing wedge resection.

— peripheral wedge or segmental resection can be by either open surgery or a closed video-assisted technique but recurrence rates tend to be higher than for more radical operations. Sleeve resections (bronchial or lobectomy) are lung sparing aimed at removal of the lesion and reanastomosis of the proximal major airway to the distal bronchial tree. Pneumonectomy is indicated when there is tumour involvement of hilar structures or the oblique fissure is traversed. Segmentectomy, sleeve resections and pneumonectomy can all be extended to include en bloc excision of involved contiguous thoracic structures. Extrapleural pneumonectomy encompasses removal of visceral and parietal pleurae, lung, ipsilateral hemi diaphragm and pericardium. Definition of an intrapericardial or extrapericardial plane of vascular resection is important in distinguishing T3 and T4 tumours.

Tumour

Site
— central (main/segmental bronchus): <2 cm or ≥2 cm from carina; RUL/RML/RLL/LUL/LLL.
— peripheral (parenchymal/pleural).

Size
— length × width × depth (cm) or maximum dimension (cm).
Squamous carcinomas can attain a large size and remain localized, whereas small cell carcinomas can be small primary lesions but with extensive local and distant spread.

Appearance
— necrosis/haemorrhage/mucoid/cavitation.
— polypoid/nodular/ulcerated/stenotic.
— endobronchial/bronchial/extrabronchial.

Squamous cell carcinoma frequently cavitates, central carcinoid is polypoid or nodular, small cell carcinoma is submucosal and bronchostenotic or shows extrinsic compression.

Edge
— circumscribed/irregular.

Pulmonary changes
— scar: peripheral adenocarcinoma.
— fibrosis/asbestosis.
— partial and hilar or total: atelectasis/obstructive pneumonitis, the extent of which helps determine the pT stage.

2. HISTOLOGICAL TYPE
Crucial therapeutic distinction is made between small cell carcinoma and non-small cell (squamous/adenocarcinoma/large cell) carcinoma.

Squamous cell carcinoma
— 40–50% of cases. Requires nuclear stratification, intercellular bridges, ±keratinization.
— large cell/small cell.
— keratinizing/non-keratinizing.

variants:

— spindle cell (see carcinosarcoma): cytokeratin positive ± vimentin positive.
— basaloid: poor prognosis, nests of palisaded basaloid cells with central comedonecrosis, hyalinised stroma.
— papillary: >70% exophytic or papillary malignant epithelial fronds with focal invasion at the base and better prognosis (70% 5-year survival).
— adenoidsquamous: usual prognosis, acantholytic (pseudoglandular) pattern.
— adenosquamous: mixed differentiation with the minor component at least 10% of the tumour. Worse prognosis. Adenocarcinoma may have obvious glands or is solid with mucin positive cells.
— clear cell.

Small cell carcinoma
— 25% of cases. Small round/fusiform nuclei (×2–3 lymphocyte size) with granular chromatin, moulding and an inconspicuous nucleolus, DNA crush and vessel artefact (Azzopardi effect), fir tree hyaline stroma, apoptosis, necrosis and mitoses. The nuclear features are the diagnostic characteristic of small cell carcinoma. Note that there can be a scattered population of large bizarre (polyploid) cells.
— oat.
— intermediate: larger nucleus/more cytoplasm and most likely represents better preserved/fixed oat cell, i.e. the same tumour.
— combined: + non-small cell component, e.g. squamous or adenocarcinoma.

Adenocarcinoma
— 15% (50% of lung cancer in females and also in non-smokers) of cases. 35% endobronchial, 65% peripheral, 75% involve the pleura at presentation and unusually can give a pseudomesotheliomatous picture. Central scar. Higher resectability rates than squamous carcinoma.
— acinar.
— papillary.
— solid with mucus formation (>5 PAS/AB-diastase positive cells in at least 2 hpfs).
— bronchioloalveolar: peripheral; single/multiple or pneumonic infiltrate with lepidic spread along alveolar walls and no stromal, vascular or pleural invasion.
— other variants: mucinous (colloid), signet ring cell, clear cell.

Large cell carcinoma
— 5–10% of cases.
— no evidence of squamous or glandular differentiation although they probably represent undifferentiated forms of these.
— giant cell, clear cell, lymphoepithelioma-like, basaloid and neuroendocrine variants.

In primary clear cell carcinoma (rare) exclude clear cell change in squamous or adenocarcinoma, secondary thyroid, salivary or renal cell carcinoma, malignant melanoma and benign clear cell (sugar) tumour of lung (HMB-45 and glycogen positive)—a perivascular epithelioid cell tumour (PEComa)).

Miscellaneous
— pulmonary endodermal tumour or adenocarcinoma of fetal type. Young patients with a solitary mass, endometrioid type glands and better prognosis.
— pulmonary blastoma: adults, peripheral, solitary and large. Well-differentiated fetal-type tubular glands in a cellular embryonal stroma and poor prognosis.
— carcinosarcoma/sarcomatoid carcinoma: pulmonary or polypoid bronchial mass. Squamous (or large cell/adenocarcinoma) with fibrosarcoma-like spindle cells (diffuse or focal cytokeratin (AE1/AE3) positive) representing monophasic sarcomatoid (spindle cell carcinoma), or biphasic with heterologous mesenchymal differentiation, e.g. cartilage, bone, striated muscle. Poor prognosis and overlaps with pleomorphic (spindle/giant cell) carcinoma. Metastases can be epithelial, sarcomatoid or mixed.

Note that only about 40% of primary lung carcinomas are of homogeneous histological type and mixed differentiation and patterns are reasonably common, e.g. squamous and small cell components, acinar and papillary adenocarcinoma.

Neuroendocrine tumours
— 5% of primary pulmonary neoplasms. See also small cell carcinoma (above).
— chromogranin, synaptophysin, CD56 (NCAM), TTF-1 positive.
— carcinoid: younger patients and polypoid, either central or peripheral. Nodal metastasis in 5–15% and 70–90% 10-year survival.
— atypical carcinoid: central/peripheral and spindle cells with cell atypia, necrosis (usually punctate) and mitoses 2–10/10 hpfs. Nodal metastasis in 50–70% with 60% 5-year survival.
— large cell neuroendocrine carcinoma: 34% 5-year survival. Significant numbers of endocrine cells present rather than just a non-small cell carcinoma with focal endocrine differentiation. Solid sheets/nests/peripheral palisading/moderate cytoplasm. A spectrum of tumours with well (carcinoid), intermediate (atypical carcinoid) and poorly differentiated (small cell/large cell) forms.

Salivary gland-type adenocarcinoma
— bronchial mucosal gland origin.

— adenoid cystic carcinoma: indolent growth but prognosis is poor with late metastases to nodes and lung parenchyma common. Along with squamous carcinoma the commonest primary tracheal tumour.
— mucoepidermoid carcinoma: prognosis is determined by the histological grade.

Metastatic carcinoma
— multiple/bilateral/well-defined/rapid growth/nodular or mass lesions: breast, gut, kidney, sarcoma, malignant melanoma, ovary, germ cell tumour.
— lymphangitis carcinomatosis: stomach, breast, pancreas, prostate, lung.
— cavitation in a mass lesion: squamous carcinoma, gut, leiomyosarcoma.
— endobronchial polypoid mass: breast, kidney, gut, sarcoma.
— vasculo-embolic: breast, stomach, liver, choriocarcinoma.
— bronchioloalveolar pattern of spread: gut, pancreas (metastases are more pleomorphic and necrotic than bronchioloalveolar carcinoma), prostate.

In limited biopsy material a positive diagnostic yield is increased by multiple biopsies (5 or 6) examined histologically through at least three levels, the aim being to designate basic neoplastic categories, e.g. primary vs. secondary, small cell vs. non-small cell carcinoma, neuroendocrine (carcinoid) lesions and lymphoma. This is due to tumour heterogeneity and poor observer agreement at subclassifying moderately to poorly differentiated cancers of non-small cell type. Designation of small cell carcinoma is reasonably robust and it must be distinguished from carcinoid (Ki-67 <5–10%), malignant lymphoma (CAM5.2, CD56, TTF-1, CD45) and small cell variant of squamous carcinoma. In this context the relatively robust preservation of immunogenicity despite extensive biopsy crush artefact is a diagnostically useful tool. The presence of carcinoma in situ and a lack of demonstrable invasion is not unusual in biopsies and must be correlated with the clinical findings. It may be representative of the lesion if derived from a segment of thickened, irregular mucosa. However, in the presence of an obvious bronchoscopic abnormality and radiological mass lesion it usually represents the edge of an invasive carcinoma. Squamous metaplasia may be entirely non-specific, associated with a carcinoma or overlying a lesion such as carcinoid tumour or small cell carcinoma, when it can be atypical and suggest an erroneous cytological diagnosis of non-small cell carcinoma in brushings material. Sometimes the main biopsy fragments are negative but dyscohesive clusters of cytologically malignant cells lie in mucous separate from the epithelial surface. Close correlation with cytology preparations, e.g. bronchial brushings and washings and transbronchial fine needle aspirates, increases diagnostic yield and accuracy with agreement rates of 70–90% for small cell carcinoma, well-differentiated squamous and adenocarcinomas. Cytology is particularly helpful where there is biopsy sampling error, extensive biopsy crush artefact, e.g. small cell carcinoma and

extrabronchial or peripheral cancers. Cell yield and preservation can be high when biopsy fragments are negative or uninterpretable. Conversely, the tissue pattern and capability for immunohistochemistry in a positive biopsy can be helpful in specific situations, e.g. primary vs. secondary adenocarcinoma, small cell carcinoma vs. lymphoma. Thoracoscopic biopsy is used for patients suspected of having malignancy but in whom bronchial biopsy and cytology are negative and in suspected bilateral disseminated disease. Other sources of a positive diagnosis are radiologically guided FNA of peripheral lung tumours, pleural fluid cytology and FNA cytology or biopsy of cervical or supraclavicular lymph nodes. These approaches should be considered when the tumour is difficult to diagnose by conventional means, the patient is unfit for bronchoscopy, or there is suspected disseminated disease. Thus a tissue diagnosis is obtained providing staging information, a basis for adjuvant therapy and exclusion of unrelated non-respiratory malignancy, e.g. malignant lymphoma.

3. DIFFERENTIATION

Well/moderate/poor/undifferentiated or Grade 1/2/3/4.

— for squamous carcinoma based on cellular atypia, keratinization and intercellular bridges.
— for adenocarcinoma based on percentage tumour gland formation (well/G1 >95%; moderate/G2 50–95%; poor/G3 <50%).

Small cell carcinoma and large cell carcinoma are by definition undifferentiated (grade 4) and have poor prognosis.

4. EXTENT OF LOCAL TUMOUR SPREAD

Border: pushing/infiltrative.
Lymphocytic reaction: prominent/sparse.
Distance to the proximal bronchial limit (mm).
Distance to the mediastinal limit (mm).
Distance to the pleura (mm).

— visceral pleural invasion is recognized by direct perforation of the mesothelium and also infiltration of the inner elastin layer in the submesothelial plane. Note that the pleura can be distorted without actual true invasion and use of an elastin stain is helpful.

Distance to the pericardium (mm).
Mucosa, cartilage plates, parenchyma.
Tumour necrosis.
The TNM classification applies to all type of lung carcinoma but not carcinoid tumour.

pTx positive cytology
pTis carcinoma in situ
pT1 tumour ≤3 cm diameter, surrounded by lung/visceral pleura and not invasive proximal to a lobar bronchus

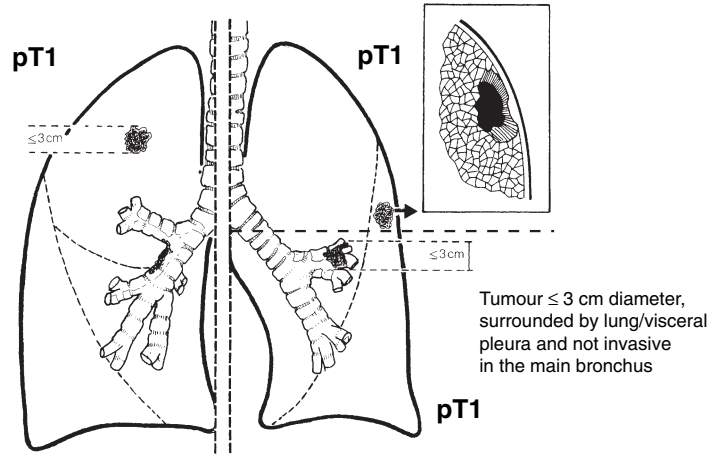


FIGURE 17.1. Lung carcinoma.

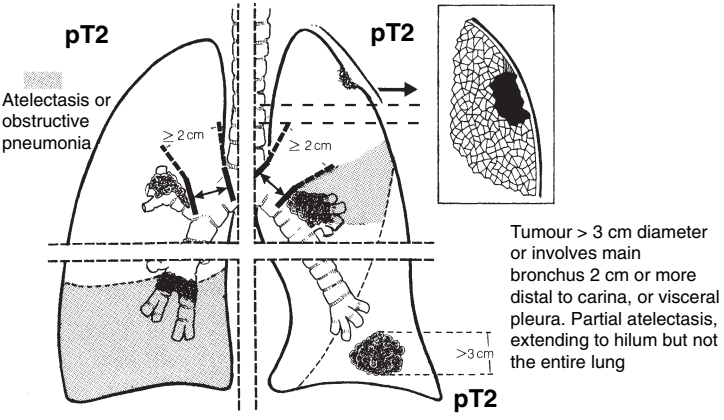


FIGURE 17.2. Lung carcinoma.

pT2 tumour >3 cm diameter or involves main bronchus 2 cm or more distal to the carina, or visceral pleura. Partial atelectasis, extending to hilum but not the entire lung

pT3 tumour of any size invading any of: chest wall, diaphragm, mediastinal pleura, parietal pericardium or tumour of main bronchus <2 cm distal to the carina or total lung atelectasis/obstructive pneumonitis

pT4 tumour of any size invading the mediastinum, heart, great vessels, trachea, oesophagus, vertebral body, carina, or tumour with

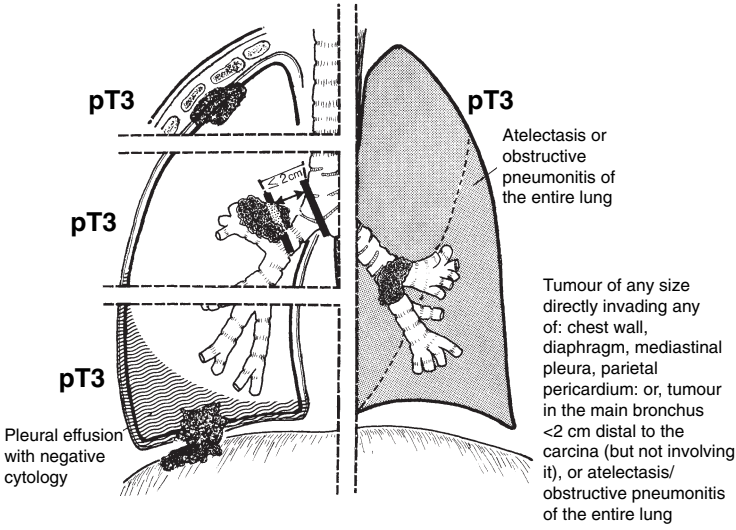


FIGURE 17.3. Lung carcinoma.

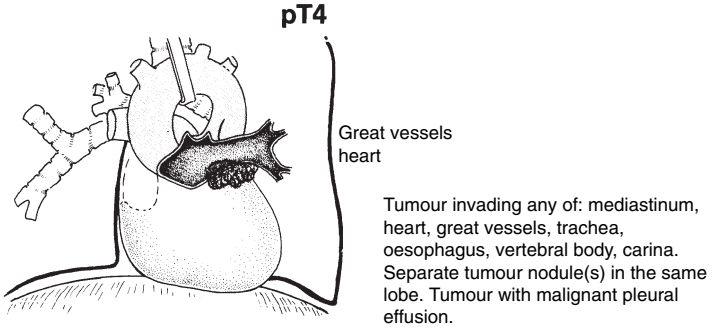


FIGURE 17.4. Lung carcinoma.

malignant pleural effusion. Separate tumour nodules in the same lobe.

Involvement of parietal pericardium, rib and phrenic nerve are pT3.

Vocal cord paralysis, superior vena cava syndrome, compression of trachea or oesophagus, involvement of visceral pericardium or discontinuous pleural deposits are classified as pT4.

Some 60–75% of lung cancers are incurable at presentation due to extensive local or distant spread with symptoms developing late in the

disease course. Spread is by direct extension along the bronchus (proximally and distally), direct into the lung parenchyma and to the mediastinum and pleura when diaphragm and chest wall may be involved. Distant metastases are commonly seen in the liver, lung elsewhere (by lymphovascular or aerogenous spread), adrenals, bone, kidney and CNS (particularly adenocarcinoma). A majority of small cell carcinomas have extensive metastatic spread at the time of diagnosis.

5. LYMPHOVASCULAR INVASION

Present/absent.
Intra-/extratumoral.
Common (80%) in lung cancer and along with nodal metastases is an adverse prognostic indicator.

6. LYMPH NODES

Site/number/size/number involved/limit node/extracapsular spread.
Regional nodes: intrathoracic, scalene, supraclavicular.
A regional lymphadenectomy will ordinarily include a minimum of six lymph nodes and the surgeon will often submit separately dissected and labelled lymph node stations.

pN0 no regional lymph node metastasis
pN1 metastasis in ipsilateral peribronchial/hilar/intrapulmonary nodes including involvement by direct extension
pN2 metastasis in ipsilateral mediastinal/subcarinal nodes
pN3 metastasis in contralateral mediastinal, contralateral hilar, ipsi-/contralateral scalene or supraclavicular nodes.
pM1 is distant metastasis and includes separate tumour nodule(s) in a different lobe (ipsilateral or contralateral) or discontinuous tumour in the chest wall or diaphragm.

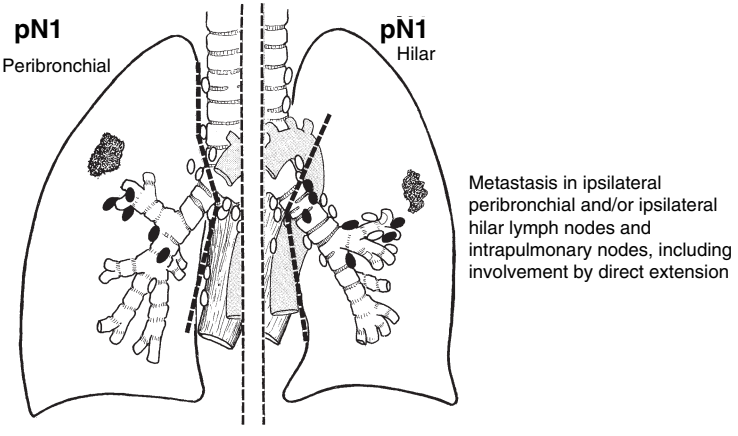


FIGURE 17.5. Lung carcinoma: regional lymph nodes.

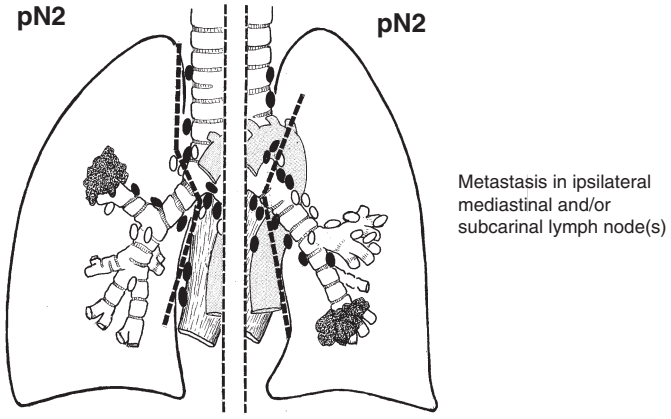


FIGURE 17.6. Lung carcinoma: regional lymph nodes.

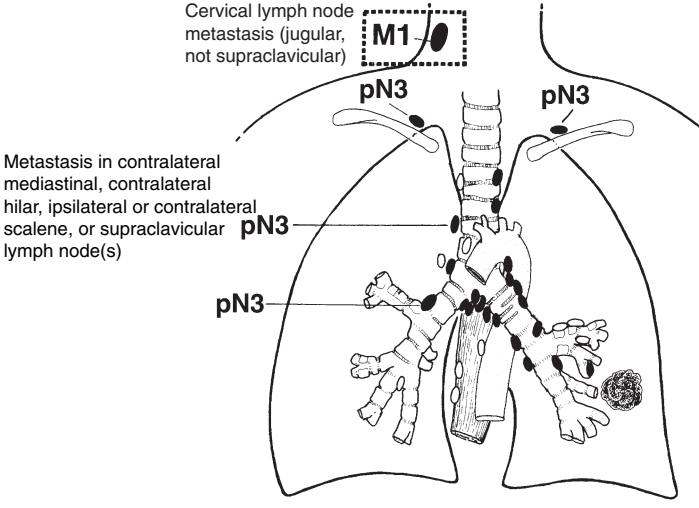


FIGURE 17.7. Lung carcinoma: regional lymph nodes.

Cervical, scalene or mediastinal lymph node FNA or biopsy is sometimes used to establish a diagnosis of carcinoma in patients suspected of having a malignancy but in whom bronchial biopsy and cytology are negative, when it represents recurrent disease, or who are medically unfit for invasive procedures.

7. EXCISION MARGINS

Distances (mm) to the proximal bronchial, vascular and mediastinal limits and pleura.

The presence of significant dysplasia at the bronchial mucosal limit can be a marker of potential local recurrence.

8. OTHER PATHOLOGY

Lymphangitis carcinomatosa: can be diagnosed on transbronchial biopsy and is characterized by involvement of peribronchial and perivascular lymphatics.

Asbestos bodies/asbestosis/mesothelioma: 5% of lung cancer deaths. Asbestos exposure can also be a co-factor for development of bronchogenic carcinoma.

Scar/fibrosis in lung periphery can predispose to or harbour adenocarcinoma.

Lung cancer is multiple (either synchronous or metachronous) in up to 5% of cases and associated with independent cancers of the head and neck region in 10–20% of cases.

Metastatic carcinoma may be single or multifocal, diffuse or nodular, endobronchial, parenchymal, lymphovascular, vasculo-embolic or pleural. Knowledge of the clinical history and direct comparison of morphology with the primary tumour are important. This can be supplemented by cytokeratin profile expression (CK7/20) and specific immune markers, e.g. thyroglobulin, PSA, CA 125 (ovary), ER/GCDFP-15 (breast), CK20/CDX-2 (colorectal), TTF-1 and surfactant antibody (50% of lung adenocarcinomas). Surgical resection of germ cell tumour and carcinomatous (e.g. colorectum) pulmonary metastases is not infrequent, the appearances of which can be greatly altered by adjuvant therapy, i.e. tumour necrosis, inflammation, fibrosis and tissue maturation. Similarly, chemotherapy of metastatic osteosarcoma can result in pulmonary nodules of mature bone with no residual malignant tissue.

Atypical adenomatous hyperplasia: usually <5 mm diameter and well demarcated from adjacent lung parenchyma, regarded as a precursor of malignancy (proposed AAH-BAC-invasive adenocarcinoma sequence) and seen in 10% (often multifocal) of resected lung carcinomas, especially peripheral or bronchioloalveolar carcinoma (BAC). BAC (usually >1 cm) is either of bronchial goblet cell, type II pneumocyte or peripheral Clara cell origin and is categorized as non-mucinous (solitary, hob nail cells, good prognosis, 60–75% of cases) or mucinous (multifocal, bilateral, worse prognosis). Surfactant antibody and TTF-1 positivity are useful for distinguishing from secondary carcinoma, e.g. large bowel. BAC has a better prognosis than other lung cancers, particularly when <3 cm diameter, and is being increasingly detected by CT/PET/FNA investigation. Thorough sampling is necessary to detect any central prognostically adverse fibrous scar that may harbour more usual type invasive adenocarcinoma.

Extrapulmonary effects: e.g. small cell carcinoma and Cushing's syndrome (ACTH), carcinoid syndrome, diabetes insipidus (ADH), gynaecomastia, hypercalcaemia.

Immunophenotype

— small cell carcinoma:
chromogranin ±, positive for synaptophysin, CD56 (NCAM), CAM5.2 (paranuclear dot reactivity), TTF-1, Ki-67 >90%, CK7.
— squamous cell carcinoma:
cytokeratin positive (AE1/AE3, CK5/6, 34βE12)
±EMA, vimentin, CEA, CK7, CAM5.2.
— spindle cell carcinoma:
cytokeratin (focal AE1/AE3) positive, vimentin positive, ±CEA, TTF-1.
— adenocarcinoma:
CAM5.2, CK7, EMA, CEA positive, vimentin, CD15, MOC-31, PE10 (50% of cases), TTF-1, Ber EP4.
— bronchioloalveolar carcinoma:
PE 10, TTF-1, cytokeratin (CAM5.2) positive. Non-mucinous is CK7+/CK20–, mucinous CK7+/CK20 +/TTF-1±.
— carcinoid:
chromogranin, TTF-1, synaptophysin, CAM5.2, Ki-67 <5–10%.

Prognosis

Prognosis in lung cancer (overall 13% 5-year survival) relates to weight loss, performance status, cell type (small cell carcinoma has 2% long-term survival and 90% present with locally advanced or systemic disease), cell differentiation (well differentiated is better than poorly differentiated) and tumour stage (only 10–20% of non-small cell carcinomas are potentially curable by resection). An important therapeutic distinction must be made between small cell carcinoma (chemotherapy) and non-small cell carcinoma (surgery ± radiotherapy). This can be achieved with a relatively high level of consistency (kappa = 0.86), whereas subtyping of non-small cell carcinoma shows poor interobserver agreement (kappa = 0.25). A general guide to suitability for surgical resection is non-small cell cancer >2 cm from the carina and without mediastinal lymph node involvement, i.e. ≤pT2 N1. International trials are currently examining the role of neoadjuvant therapy in non-small cell carcinoma more advanced than stage pT2 N1. The significance of occult bone marrow micrometastases detected by immunohistochemistry is uncertain. Prognosis improves if the carcinoma is "early" or "occult" with positive cytology but negative chest radiology: preoperative chemotherapy may also be beneficial.

Operable (localized)	5-year survival
Squamous/large cell	35%
Adenocarcinoma	
well differentiated	75%
poorly differentiated	35%
overall	50%
Small cell	10%

Non-operable (extensive)	5-year survival
Squamous cell	6%
Small cell	2%

10. OTHER MALIGNANCY

Leukaemia
— 50–60% of acute leukaemias.
— 15–40% of chronic leukaemias.
— rarely granulocytic sarcoma; CD 68/chloroacetate esterase/myeloperoxidase positive.

Lymphoma
— primary MALToma or diffuse large B-cell lymphoma (5–20% of cases) or secondary to nodal/systemic disease. Designation depends on the constituent cell type and clinicopathological staging of the extent of disease. There may also be a previous history of nodal lymphoma.

MALT lymphoma
— commonest primary lung lymphoma.
— sixth/seventh decade.
— ± Sjögren's syndrome or rheumatoid arthritis.
— central mass with peripheral tracking along septa, bronchovascular bundles and pleura.
— solitary or multifocal ± spread to other MALT sites.
— limited resection ± chemo-/radiotherapy.
— 5-year survival 80–90%, most are low grade but can transform to high grade (40–60% 5-year survival).
— some large B-cell (high grade) pulmonary lymphomas probably originate in low-grade MALToma.

High-grade lesions are easily assessed as malignant but must be distinguished from other tumours, e.g. non-small cell carcinoma, using immunohistochemistry. Low-grade lesions are characterized by a dense monomorphic interstitial population of centrocyte-like cells, absence or colonization of reactive follicles, lymphoepithelial lesions and local invasion. B-cell predominance, light chain restriction and immunoglobulin heavy/light chain monoclonal gene rearrangements are confirmatory in distinction from a lymphoid interstitial pneumonitis, nodular lymphoid hyperplasia or follicular bronchiolitis. Mass lesions previously designated pseudolymphoma are now considered to be low-grade MALTomas.

Primary or secondary Hodgkin's disease
— usually secondary to spread from mediastinal disease.
— parenchymal nodules or endobronchial plaque/nodules.

T-cell-rich large B-cell lymphoma (EBV related)
— on a spectrum with B-cell lymphomatoid granulomatosis/angiocentric immunoproliferative lesion and associated with EBV.

— polymorphous (lymphocytes, plasma cells, histiocytes) angiocentric/destructive infiltrate containing atypical lymphoid cells.
— prognosis (poor) is dictated by the histological grade (number of atypical cells) and extrapulmonary lesions are common (kidneys, liver, brain, spleen).

Intravascular lymphoma
— malignant angioendotheliomatosis or angiocentric large B-cell lymphoma: skin, CNS and adrenal gland involvement with poor prognosis.

Post-transplant lymphoproliferative disorder (PTLD)
— EBV-associated spectrum of lymphoproliferation (immortalized B cells) following (first 2 years) immunosuppression for solid organ or bone marrow transplantation and occurring in the native or transplant lung.
— can respond to reduction of immunosuppression and antiviral therapy.
— early (plasma cell hyperplasia), polymorphous (infectious mononucleosis-like) or monomorphic (as in large B-cell lymphoma) stages. Also shows angioinvasion and necrosis.
— monomorphic/monoclonal lesions are worse prognosis than polymorphic/polyclonal lesions.
— diagnosis by chest X-ray, CT scan, transthoracic needle biopsy, morphology, immunophenotype, clonality (PCR) and EBV status (in-situ hybridization).

Epithelioid haemangioendothelioma (intravascular bronchioloalveolar tumour)
— a vascular tumour of intermediate-grade malignancy (CD31/CD34 positive) in young adult females. Slow progression and association with liver and skin lesions.

Kaposi's sarcoma
— AIDS.

Angiosarcoma
— primary or secondary.

Malignant melanoma
— usually secondary, intraparenchymal or endobronchial.

Sarcomas including synovial sarcoma, leiomyosarcoma, rhabdomyosarcoma (embryonal children, pleomorphic adults)
In any lung sarcoma it is important to exclude the more common possibilities of either a primary elsewhere or a lung carcinoma with sarcoma-like morphology. Endobronchial sarcoma presents earlier with better prognosis than intrapulmonary sarcoma.

18
Malignant Mesothelioma

1. GROSS DESCRIPTION

Specimen

— pleural, peritoneal or laparoscopic aspiration cytology or biopsy/thoracoscopic or open biopsy/pleurectomy/extrapleural pneumonectomy/omentectomy.
— size (cm) and weight (g).
— pleural disease can be asymptomatic or present with pain, breathlessness or general systemic effects, e.g. weight loss. Pleural plaques, thickening and calcification are demonstrated by chest X-ray and CT scan. Thoracentesis or pleural fluid aspiration can be diagnostic or therapeutic for symptomatic relief. Percutaneous closed needle biopsy is diagnostic in a minority of cases (30–50%) and may need to be supplemented by CT-guided thoracoscopic biopsy or open pleural biopsy. The latter may be allied to decortication or stripping of the constricting visceral peel. Chest wall biopsy site seeding is a particular problem for which preventative radiotherapy is used. Pleurectomy attempts to debulk the mesothelioma providing multiple strips of pleural membrane. Extrapleural pneumonectomy is en-bloc resection of the pleurae, lung, ipsilateral hemidiaphragm and pericardium. Peritoneal disease may present with ascites and a tissue diagnosis is obtained by peritoneal fluid cytology, laparoscopic or open biopsy.

Tumour

Site

— pleural (parietal/visceral)/pericardial/peritoneal.
— pleura (>80%) is the commonest site, then peritoneum (10–15%).

Size

— length × width × depth (cm) or maximum dimension (cm).

Appearance

— localized (solitary)/diffuse/nodular/plaque/infiltrative/cystic change.

Edge

— circumscribed/irregular.

2. HISTOLOGICAL TYPE

Adenomatoid tumour

— benign: circumscribed pale nodule in the epididymis, fallopian tube or uterine myometrium with or without a serosal connection. Microcystic pattern of mesothelial proliferation with intervening smooth muscle prominence.

Localized solitary fibrous tumour

— rare/solitary/visceral pleura, circumscribed/ smooth or bossellated.
— "patternless" fibroblasts and vessels with bland cytology, 90% benign, CD34 positive.
— now regarded as arising from subserosal fibroblasts/mesenchymal cells rather than from mesothelium and is encountered in other organs.

Multicystic peritoneal mesothelioma (Multilocular Peritoneal Inclusion Cysts)

— on the surfaces of the uterus, ovary, bladder, rectum and pouch of Douglas it is potentially locally recurrent and, rarely, present in retroperitoneum, bowel mesentery and wall. Differential diagnosis of lymphagitic (lining cells are cytokeratin negative) and unilocular peritoneal inclusion cysts, and cystic adenomatoid tumour or malignant mesothelioma. Fifty percent recur over many years and can occasionally lead to death. Some have a previous history of surgery, endometriosis or pelvic inflammatory disease.

Well-differentiated papillary peritoneal mesothelioma

— middle-aged women. Rare, with most being an incidental finding at hysterectomy. Localized and benign but can be extensive and diffuse nodular serosal/omental disease with ultimately progression and ascites. Rarely pleural based.

Diffuse malignant mesothelioma

— main varieties are epithelial (epithelioid), sarcomatoid and biphasic. Rarer types are desmoplastic, small cell, lymphohistiocytoid, decidual and undifferentiated or anaplastic.
— epithelial (50%):
    tubulopapillary
    microglandular
    solid (epithelioid)
    small cell 6%
    pleomorphic (large cell)
    lymphohistiocytoid 1%: aggressive
    deciduoid
    clear cell
    signet ring cell.
— sarcomatoid (15%):
    fibrosarcomatous-like/cellular storiform
    fibrous (desmoplastic) 5–10%

angiomatoid
chondroid/osteoblastic/rhabdomyoblastic/leiomyoid.
— mixed (biphasic) (25%).

Metastatic carcinoma
— the commonest malignant tumour of the pleura.
— lung/breast/stomach/ovary/prostate/kidney carcinomas, malignant melanoma, soft tissue sarcoma and germ cell tumours can all mimic mesothelioma on histology, and even gross distribution of disease (pseudomesotheliomatous picture). Knowledge of relevant previous history and close clinicopathological correlation with comparison of tumour morphology and immunohistochemistry are needed.

3. DIFFERENTIATION

Well/moderate/poor.

— no formal grading system and probably best regarded as a minority of well-differentiated lesions (e.g. papillary and multicystic peritoneal variants) and others which are not graded. Sarcomatoid mesotheliomas are considered poorly differentiated, epithelial as well to moderately differentiated.

4. EXTENT OF LOCAL TUMOUR SPREAD

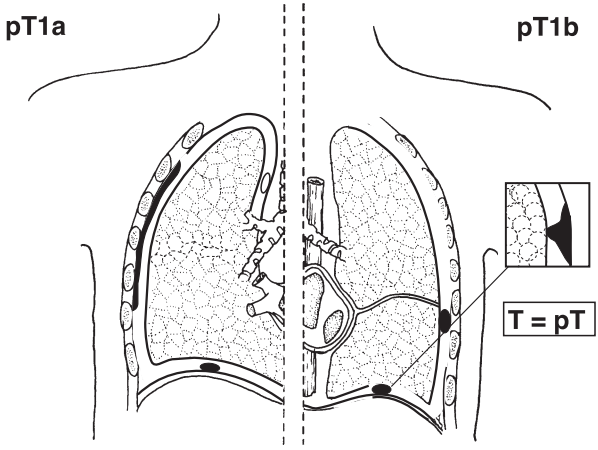
Border: pushing/infiltrative.
Lymphocytic reaction: prominent/sparse.
The TNM classification applies to pleural mesothelioma only.

pTis carcinoma in situ
pT1 tumour involves ipsilateral parietal (mediastinal, diaphragmatic) pleura
a. no involvement of visceral pleura
b. focal involvement of visceral pleura
pT2 tumour involves ipsilateral pleural surfaces with also any of: confluent visceral pleural tumour, invasion of the diaphragmatic muscle or lung parenchyma
pT3* tumour involves ipsilateral pleural surfaces with also any of: invasion of endothoracic fascia, mediastinal fat, solitary chest wall soft tissue focus, non-transmural pericardial involvement
pT4† tumour involves ipsilateral pleural surfaces with also any of: contralateral pleura, peritoneum, rib, extensive chest wall or mediastinal invasion, myocardium, brachial plexus, spine, transmural pericardium, malignant pericardial effusion.

Spread is typically pleural, encasing the lung with extension along fissures and septa and into subpleural lung parenchyma. Nodal spread and distant metastases (up to 30% of cases) occur late in the disease course.

Contiguous spread through the diaphragm with involvement of abdominal organs is not infrequent.

*Locally advanced but potentially resectable tumour.
†Locally advanced but technically unresectable tumour.



Tumour involves ipsilateral parietal pleura with or without focal involvement of visceral pleura
a. Tumour involves ipsilateral partietal (mediastinal, diaphragmatic) pleura. No involvement of visceral pleura
b. Tumour involves ipsilateral parietal (mediastinal, diaphragmatic) pleura, with focal involvement of visceral pleura

FIGURE 18.1. Pleural malignant mesothelioma.

Tumour Involves any of the ipsilateral pleural surfaces, with at least one of the following:

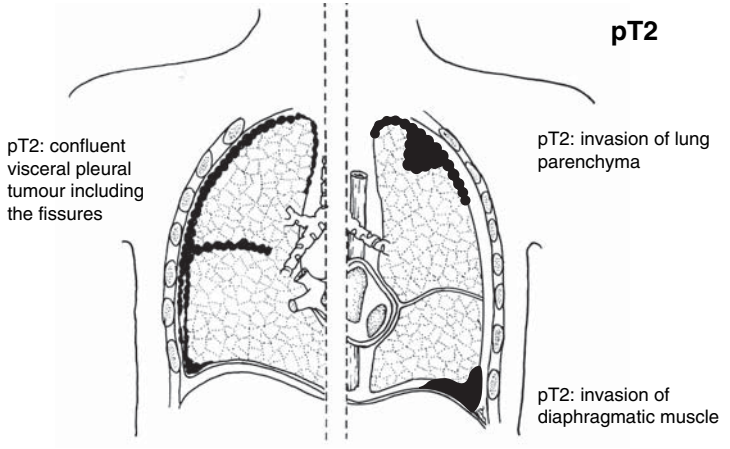


FIGURE 18.2. Pleural malignant mesothelioma.

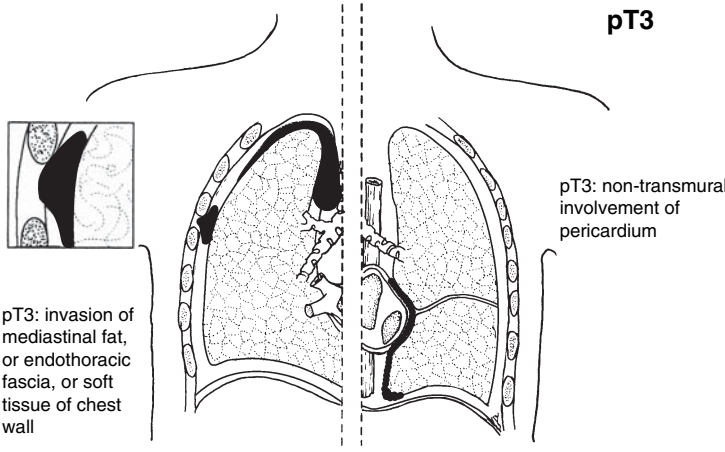


FIGURE 18.3. Pleural malignant mesothelioma.

Peritoneal disease is usually secondary to pleural tumour but can also be primary and asbestos related. Pericardial disease usually represents spread from pleural tumour.

Flat or granular pleura adjacent to tumour nodules may show cytological atypia constituting "mesothelioma in situ" and, although unusual in pleural biopsies, this can be a useful indicator of potential for progression to invasion or concurrent tumour.

5. LYMPHOVASCULAR INVASION

Present/absent.
Intra-/extratumoral.

6. LYMPH NODES

Site/number/size/number involved/limit node/extracapsular spread.
Regional nodes: intrathoracic, internal mammary, scalene, supraclavicular.

pN0 no regional lymph node metastasis
pN1 metastasis in ipsilateral bronchopulmonary and/or hilar lymph node(s), including involvement by direct extension
pN2 metastasis in subcarinal lymph node(s) and/or ipsilateral internal mammary or mediastinal lymph node(s)
pN3 metastasis in contralateral mediastinal, internal mammary, hilar node(s), and/or ipsilateral or contralateral scalene or supraclavicular lymph node(s).

7. EXCISION MARGINS

Distance (mm) to the nearest painted excision margin of local resection for limited disease.

8. OTHER PATHOLOGY

Pleural plaques, subpleural fibrosis, asbestosis, bronchogenic carcinoma requiring increasing levels of asbestos exposure, respectively.

Two to three percent of people with exposure to significant amounts of asbestos develop malignant mesothelioma. The consequences of asbestos exposure depend on the fibre type (amphiboles, e.g. crocidolite are particularly pathogenic) and can be both dose-related and idiosyncratic. Some individuals require less exposure to develop asbestos-related disease while others with extensive fibre burden do not. Classically there is a long lag period of 20–50 years until illness develops. Exposure can also be second-hand, e.g. washing a spouse's contaminated clothing. Fibre burden can be assessed by incineration of lung tissue and quantification by scanning electron microscopy. Identification of ferruginous asbestos bodies by light microscopy correlates with a significant fibre load. Exposure is usually occupation related. A typical clinical history of mesothelioma is a unilateral opaque chest radiograph with necessity for multiple, repeated pleural taps. Note that the tumour may infiltrate chest wall through the biopsy needle track.

Immunophenotype

A number of malignant tumours metastatic to the pleura can mimic malignant mesothelioma. These include, amongst others, adenocarcinoma of lung, spindle cell carcinoma/carcinosarcoma of lung, renal cell carcinoma, malignant melanoma, lymphoma and leukaemia, ovarian carcinoma, thymoma and sarcoma. There is no one specific marker for mesothelioma and diagnosis often relies on exclusion of metastatic carcinoma and sarcoma by immunohistochemistry, clinical history, examination and radiology. Radiology is very useful in demonstrating the distribution of disease, e.g. diffuse pleural thickening vs. an intrapulmonary/hilar mass with pleural thickening (lung carcinoma) or multiple discrete lung nodules with pleural thickening (metastatic carcinoma).

Useful immune marking is positivity with one or more of CEA, BerEP4, MOC-31, TTF-1, E-cadherin and Leu M1 (CD15) (Table 18.1), indicating adenocarcinoma and excluding mesothelioma (although some cases can be BerEP4 positive). Putatively positive mesothelioma markers that are negative in lung adenocarcinoma are CK5/6, calretinin, thrombomodulin, HBME-1, N-cadherin and WT-1. EMA usually shows strong membranous positivity in epithelial mesothelioma. A practical panel for diagnostic use is CEA, BerEP4, TTF-1, MOC-31, EMA, CK5/6 and calretinin ± thrombomodulin and WT-1

Adenocarcinoma may be mucicarmine positive/PAS-diastase resistant for mucin (60% of cases). Distinction of mesothelioma from other non-small cell lung cancers is usually by morphology as there can be overlap in cytokeratin profiles, e.g. squamous carcinoma is CK5/6 positive.

Table 18.1 Immunoexpression in mesothelial proliferations

Antibody	Epithelial mesothelioma	Reactive mesothelial cells	Pulmonary adenocarcinoma
Cytokeratin	+	+	+
Vimentin	+	±	±
EMA	+	−	+
CK5/6	+	+	−
HBME-1	±	+	−
Thrombomodulin	±	−	−
Calretinin	+	+	−
WT-1	+	+	−
CEA	−	−	+
Leu M1 (CD15)	−	−	+
BerEP4	−	−	+
TTF-1	−	−	+
E-cadherin	−		+
N-cadherin	+		−

Sarcomatoid mesothelioma may co-express cytokeratin, vimentin and muscle-specific actin. Differential diagnosis is spindle cell lung carcinoma and primary or secondary sarcoma with similar immunophenotypic co-expression, e.g. epithelioid vascular tumours, leiomyosarcoma or synovial sarcoma. Desmoplastic mesothelioma (>50% of the tumour is poorly cellular fibrous tissue) must be distinguished from fibrous pleurisy (inflammatory and reactive looking) and pleural plaque (acellular basket-weave pattern of collagen), neither of which shows parenchymal or chest wall infiltration or strongly cytokeratin positive spindle cells diffusely throughout the full depth of the fibrous tissue. Solitary fibrous tumour (CD34 positive, cytokeratin negative) should also be considered.

Other markers include:

— S100, HMB-45, melan-A (melanoma).
— CD45, CD20, CD3 (B/T-cell lymphoma).
— thyroglobulin, CK19, TTF-1, ret (thyroid papillary carcinoma).
— CA125, CK7, WT-1 (ovarian serous carcinoma).
— PAS, cytokeratin, EMA, vimentin, CD10, abdominal ultrasound/CT scan (renal cell carcinoma).
— PSA, PSAP (prostate carcinoma).
— βHCG, AFP, CD30, PLAP (germ cell tumour).
— ER/PR, GCDFP-15, CK7 (breast carcinoma).
— CEA, CK20, CDX-2 (gut carcinoma).
— CA 19-9, CK7, CK20, CA125 (pancreatic carcinoma).

Morphological markers of mesothelial malignancy vs. reactive mesothelial hyperplasia are: cytological atypia and cellularity, necrosis and invasion of subpleural connective tissue, i.e. the extent, atypia and invasiveness of the mesothelial cell population in an adequate specimen. Malignant mesothelial cells also express p53 and EMA but, unlike reactive mesothelial cells, are negative for desmin. In a significant minority

of cases diagnosis may not be able to be made at first presentation but the possibility raised from a constellation of atypical features in the pleural fluid cytology and biopsy.

Reactive mesothelial hyperplasia and dense inflammatory fibrosis do not clinically progress as does mesothelioma with repeated clinical presentations and the need for symptomatic relief by paracentesis. Some well-differentiated lesions pursue such a biological course over a span of several years but normally the clinical progression is relatively rapid, indicating a malignant diagnosis. Reactive mesothelial hyperplasia may be seen in pulmonary infarction, tuberculous pleuritis, rheumatoid arthritis, systemic lupus erythematosus and overlying primary or secondary neoplasms.

Prognosis

Prognosis of diffuse malignant mesothelioma relates to stage but is generally poor, with the majority of patients dying from their disease within 1–3 years. Spindle cell tumours are more aggressive than epithelial variants. Adjuvant chemotherapy combined with resection of limited disease (pleural decortication or pleuropneumonectomy) can occasionally result in prolonged remission with 3-year survival rates 15–30%, but only a small minority of patients are suitable. Symptomatic relief may be gained by multiple paracentesis of malignant pleural or peritoneal fluid supplemented by intracavitary chemotherapy. This may act either directly on the tumour cells, reducing secretions, or produce a loculated, sclerosant effect. Palliative radiotherapy and chemical (talc) pleurodesis also have roles to play. The former can induce bizarre multinucleated tumour cell forms and the latter a pseudosarcomatous biphasic pattern. Iatrogenic wound site implantation metastases can also occur in 15–20% of cases. Well-differentiated multicystic and papillary peritoneal mesotheliomas are regarded as being of borderline or low malignant potential.

9. OTHER MALIGNANCY

— epithelioid haemangioendothelioma, angiosarcoma, synovial sarcoma.
— thymoma.
— desmoplastic small cell tumour.
— malignant lymphoma: secondary to a lymphoproliferative disorder (e.g. CLL), nodal or systemic disease, or primary, e.g. the rare pyothorax or effusion associated lymphomas (large B-cell lymphomas: EBV and HHV8/immunodeficiency associated, respectively).

19
Mediastinal Cancer

1. GROSS DESCRIPTION

Specimen

— percutaneous or thoracoscopic fine needle aspirate/(needle core) biopsy/resection (cervical thymectomy or thoracotomy).
— number of fragments and their length (mm).
— size (cm) and weight (g).

Tumour

Site

— mediastinal boundaries:

lateral	pleural cavities
anterior	sternum
posterior	spine
superior	thoracic inlet
inferior	diaphragm.

— superior:
  thymoma and thymic cysts
  malignant lymphoma
  nodular goitre thyroid
  ectopic parathyroid lesions.
— anterior:
  thymoma (75% of cases) and thymic cysts
  carcinoid tumours
  malignant lymphoma
  germ cell tumours
  metastatic carcinoma
  thyroid/parathyroid lesions
  mesenchymal lesions—lipoma, lymphangioma, haemangioma.
— middle:
  metastatic carcinoma
  malignant lymphoma
  pericardial/bronchogenic cysts
  primary cardiac tumours.
— posterior:

neural tumours—neurilemmoma, neurofibroma, ganglioneuroma, ganglioneuroblastoma, malignant schwannoma, neuroblastoma, paraganglioma
gastroenteric cysts.

Size
— length × width × depth (cm) or maximum tumour dimension (cm).

Appearance
— circumscribed/encapsulated/infiltrative/fleshy/pale/pigmented/cystic/necrotic/haemorrhagic, e.g. thymoma can be encapsulated or infiltrative, solid/cystic or multiloculated, whereas lymphoma is fleshy and pale ± necrosis and sclerosis. Teratoma can be cystic, solid, necrotic or haemorrhagic. Neurilemmoma is encapsulated ± cystic degeneration.

Edge
— circumscribed/irregular.

2. HISTOLOGICAL TYPE

Metastatic carcinoma
— the commonest malignant mediastinal tumour (particularly in the middle mediastinum) and can mimic a primary thymic tumour both clinically and radiologically, e.g. small cell carcinoma lung can have a small primary lesion with extensive direct or nodal spread to the mediastinum.
— direct spread: lung, oesophagus, pleura, chest wall, vertebra, trachea.
— distant spread: breast, thyroid, nasopharynx, larynx, kidney, prostate, testicular (or ovarian) germ cell tumour, malignant melanoma.

Identify a residual nodal rim of lymphoid tissue at the tumour edge to indicate metastasis.

Malignant lymphoma
— 10–15% of mediastinal masses in the adult and occurs in decreasing order of frequency in the anterior, superior and middle mediastinum. It is the commonest primary neoplasm of the middle mediastinum. Thymic or nodal based. Specific thymic/mediastinal features are:

Hodgkin's disease: young females. Nodular sclerosis in type and fibrotic/lobulated ± thymic epithelial cysts with lacunar cells (CD15/30 positive). Radiotherapy and prognosis depend on the stage of disease.

Lymphoblastic lymphoma: acute dyspnoea in adolescent males. Mediastinal plus cervical/supraclavicular and axillary disease; ±Hassall's corpuscles and can therefore mimic thymoma. Small to medium-sized lymphoid cells, apoptosis, tdt positive—usually T cell (CD 3) and high (>95%) Ki-67 index.

Mediastinal large B-cell lymphoma: young females presenting with superior vena cava syndrome. Sclerosis/fibrosis—banded and pericellular. CD45, CD20 positive, Ki-67 positive in >70% of cells; also CD30, bcl-6 and CD10, the latter suggesting a follicle centre cell origin. Spread to pericardium, pleura, lung, sternum and chest wall common.

MALToma: occasionally.

Germ cell tumours

— 20% of mediastinal tumours/cysts.
— thymus based with a primary origin in extragonadal germ cells.
— exclude metastases from a clinical or occult testicular/ovarian germ cell tumour, particularly if there is associated retroperitoneal disease.
— mature cystic teratoma: the commonest mediastinal germ cell tumour and similar to that in the ovary.
— immature teratoma: rare; immature epithelium, mesenchyme or neural elements.
— mature and immature teratoma generally have a benign course if completely resected (adult immature teratoma is more aggressive).
— embryonal carcinoma, yolk sac tumour, choriocarcinoma (third decade, gynaecomastia)—all require chemotherapy and are less responsive with a higher relapse rate and lower survival than equivalent testicular lesions. There is also a higher rate of somatic-type malignant transformation, e.g. adenocarcinoma, angiosarcoma, rhabdomyosarcoma than in gonadal germ cell tumours. Serum HCG and AFP levels are raised in >90% of non-seminomatous germ cell tumours and high levels are an adverse prognostic indicator.
— seminoma: PLAP, CD117 positive, cytokeratin negative and 69% 10-year survival. The seminoma cells can be obscured by granulomatous inflammation, reactive lymphoid follicular hyperplasia or thymic epithelial cysts and immunomarkers are helpful.
— chemotherapy of germ cell tumour results in necrosis. Residual tumour can regrow and follow-up radiology, serum tumours markers and surgical excision are carried out.

Neurogenic tumours

— posterior mediastinum.
— children: derived from the sympathetic nervous system: neuroblastoma, ganglioneuroblastoma, ganglioneuroma.
— adults: derived from the peripheral nervous system: neurilemmoma, neurofibroma ± cystic degeneration. Malignant peripheral nerve sheath tumour: de novo or in von Recklinghausen's disease, ±enteric glands, ±rhabdomyoblasts (Triton tumour). Poor prognosis with pleural and pulmonary spread.

Sarcoma

— rarely primary: liposarcoma, synovial sarcoma.
— rhabdomyosarcoma especially alveolar (desmin/myo D1/myogenin positive).

Thymoma

— anterosuperior mediastinum.
— solid, yellow/grey, lobulated ± cystic change: 80% are encapsulated and easily excised, 20% are infiltrative. It comprises a dual population of cytokeratin positive epithelial cells and T marker (CDs 1, 3, 4, 8, 99, 1a) positive lymphocytes of variable maturity. Classification which can reflect invasiveness and prognosis relies on:
  1. the character of the epithelial cells and lymphocytes
  2. the relative proportion of these cells
  3. their cellular atypia, and
  4. the organoid architecture: lobulated corticomedullary differentiation; epithelial lined glands and cysts; Hassall's-like corpuscles; perivascular spaces.

Individual tumours can show some heterogeneity in these features. The classification according to Müller-Hermelink is:

Medullary (6%):
  spindle shaped epithelial cells
  scanty to moderate numbers of mature lymphocytes
  thick capsule
  excellent prognosis.
Mixed (composite) (20%):
  elderly patients, thick capsule, excellent prognosis
  biphasic, lobulated
  medullary component plus component of round to stellate epithelial cells (vesicular nucleus, inconspicuous nucleolus) with numerous lymphocytes.
Predominantly cortical (organoid) (7%):
  lymphocyte rich, organoid corticomedullary areas (thymus-like)
  less prominent epithelial component and expansile edge with local invasion common.
Cortical (42%):
  young patients
  large round/polygonal epithelial cells with vesicular nucleus
  lesser component of intervening immature lymphocytes
  lobulated, fibrous septa, locally invasive.
Well-differentiated thymic carcinoma (17%):
  predominantly epithelial (small cells with mild nuclear atypia)
  few lymphocytes
  lobulated, sclerotic, invasive.
Thymic carcinoma (8%):
  clear-cut cytological features of malignancy
  exclude metastasis from lung or elsewhere
  90% are either squamous cell carcinoma (± keratinization): also lymphoepithelioma-like carcinoma (similar to that of nasopharyngeal carcinoma).
Others:
  spindle cell carcinoma (carcinosarcoma)
  clear cell carcinoma

basaloid carcinoma
mucoepidermoid carcinoma
papillary carcinoma
small cell carcinoma
undifferentiated and neuroendocrine large cell carcinoma
carcinoid (classic/spindle cell/pigmented/with amyloid/atypical).

Comparison of the above with the WHO types A, B, C classification is as follows:

type A	medullary
type B	predominantly cortical (B1), cortical (B2) and well-differentiated thymic carcinoma (B3)
type AB	mixed
type C	thymic carcinoma and its variants.

3. DIFFERENTIATION/GRADE

Metastatic carcinoma
— well/moderate/poor/undifferentiated.

Malignant lymphoma
— low-grade: MALToma.
— high-grade: diffuse large B-cell lymphoma; lymphoblastic lymphoma.

Germ cell tumours
— seminoma.
— non-seminomatous: mature/immature; malignant, e.g. embryonal carcinoma, yolk sac tumour, choriocarcinoma, or with somatic malignancy.

Neurogenic tumours
— small round blue cell: neuroblastoma component.
— low-grade/high-grade: sarcoma.

Thymoma
— see above.

4. EXTENT OF LOCAL TUMOUR SPREAD

Border: pushing/infiltrative.
Lymphocytic reaction: prominent/sparse.
For all tumours:
— confined to the mediastinal nodes.
— confined to the thymus.
— into the mediastinal connective tissues.
— into other organs, e.g. pleura, lung, pericardium, main vessels.

Thymoma
I encapsulated: macroscopically and no microscopic capsular invasion

II minimally invasive: with either a. microscopic invasion into capsule, or b. macroscopic adhesion, or invasion into surrounding fatty tissue or mediastinal pleura
III widely invasive and/or implants: into neighbouring organs, e.g. pericardium, great vessels and lung
IV metastatic: with either a. widespread discontinuous pleural or pericardial dissemination, or b. lymphogenous or haematogenous disease.

I–IV equate to pT1–pT4 under a proposed TNM staging system, with III encompassing pT3, IVa equating to pT4, and IVb including pN1–3 and pM1. Lymphohaematogenous metastases, e.g. cervical nodes, lung, liver, bone and ovary can occur after a lag period of months to years post diagnosis.

5. LYMPHOVASCULAR INVASION
Present/absent.
Intra-/extratumoral.

6. LYMPH NODES
Site/number/size/number involved/limit node/extracapsular spread.
Regional nodes: intrathoracic, scalene, supraclavicular nodes

Thymoma
pN0 no regional lymph nodes involved
pN1 metastasis to anterior mediastinal lymph nodes
pN2 metastasis to intrathoracic lymph nodes other than the anterior mediastinal lymph nodes
pN3 metastasis to extrathoracic lymph nodes.

7. EXCISION MARGINS
Distances (mm) to the nearest painted margins of excision.

8. OTHER PATHOLOGY
Mediastinal neoplasms are often asymptomatic (50% of cases) and can present in a number of ways:

1. during staging or follow up (chest radiograph, CT or MRI scan) of a patient with a known cancer elsewhere, e.g. lung carcinoma, colorectal carcinoma, non-Hodgkin's lymphoma/Hodgkin's disease, or testicular/ovarian germ cell tumour
2. as an incidental finding on chest radiograph in a patient who may or may not have ill-defined symptoms, e.g. dyspnoea
3. as a finding in the investigation of a patient with other presenting features, e.g. pneumonia or pleural effusion
4. as superior vena cava syndrome due to malignant infiltration or compression of local structures, e.g. lung carcinoma (primary or secondary), malignant lymphoma
5. as a paraneoplastic syndrome, e.g. myasthenia gravis, ACTH (adrenocorticotrophic hormone) or inappropriate ADH (antidiuretic hormone) secretion.

Therefore, knowledge of a relevant past medical history is fundamental in determining the nature of the underlying abnormality. Tissue diagnosis is often obtained by CT-guided percutaneous/thoracoscopic/transbronchial FNA or needle core biopsy with material provided not only for routine morphology but, importantly, ancillary techniques such as immunohistochemistry to aid distinction between diagnoses such as metastatic carcinoma, lymphoblastic or large cell lymphoma and thymoma. However, in some cases, due to the limitations of these sampling techniques, invasive mediastinal incisional biopsy may be required. Prior to this it should be determined whether a more convenient source of tissue diagnosis is available, e.g. palpable supraclavicular or cervical lymphadenopathy or pleural fluid cytology. Needle core biopsy of a thymoma is also contentious due to disruption of the tumour capsule and the possibility of seeding into the operative site.

Tumour site within the mediastinum is an important clue to tumour type, e.g. middle mediastinal disease is most likely to be metastatic carcinoma or malignant lymphoma, whereas anterosuperior mediastinal lesions are more likely to be thymus-based cancers, e.g. thymoma, germ-cell tumours and lymphoma.

Associations

Thirty to forty-five percent of thymoma patients have myasthenia gravis—muscular fatigability of the proximal limbs and head and neck, acetylcholine receptor antibody. Other paraneoplastic syndromes relate to the mediastinal cancer type, e.g. small cell lung carcinoma with ACTH or inappropriate ADH secretion.

Thymic carcinoid tumour is associated with carcinoid tumour at other sites, e.g. bronchus, ileum and MEN I syndrome. Typically ribbons, rosettes, and balls of cells with central necrosis and calcification.

Immunophenotype

— metastatic carcinoma: cytokeratins, CEA, EMA, BerEP4, MOC-31, TTF-1, CD15 (Leu M1), ±vimentin.
— Hodgkin's disease: CD15, CD30.
— non-Hodgkin's lymphoma: CD45, CD20, CD3, CD30, κ/λ light chain restriction, molecular gene rearrangements.
— lymphoblastic lymphoma: tdt, CD10, CD99 (O 13), CD3, Ki-67 > 95%.
— seminoma: PLAP, CD117 (cytokeratin negative).
— embryonal carcinoma/yolk sac tumour: cytokeratins, HCG, AFP, CD30, (± PLAP—in embryonal carcinoma).
— thymoma: cytokeratins, EMA, CEA, S100 positive interdigitating reticulum cells; variably mature T lymphocytes CDs 1, 3, 4, 8, 99, 1a. Thymic carcinoma cells retain CD5 positivity.
— carcinoid: chromogranin, synaptophysin, CD56, ± CAM5.2.

Cystic change

— unilocular thymic cysts: developmental and thin non-inflamed wall with cubocolumnar epithelial lining.

— multilocular thymic cysts: multilocular and adherent to mediastinal structures due to inflammation and fibrosis mimicking an invasive thymic tumour. Cubocolumnar or squamous epithelial lining.
— 50% of thymic nodular sclerosing Hodgkin's disease.
— thymic seminoma.

Prognosis

Prognosis obviously relates to the nature of the underlying pathological abnormality and to whether it represents primary or secondary disease. Cancer subtype also determines the choice of therapy, e.g. surgery, chemotherapy or radiotherapy. Note that prebiopsy or presurgical radiotherapy and chemotherapy can induce tumour apoptosis, necrosis and hyalinization, which can lead to difficulties in accurate classification of disease.

In thymoma several rules apply:

1. tumours with predominantly bland spindle/oval cells are usually encapsulated and of excellent prognosis
2. tumours with predominantly round/polygonal epithelial cells have a course related to the relative predominance of epithelial cells over lymphocytes and any cellular atypia that is present, and
3. the encapsulation of the tumour, or its lack of encapsulation and any signs of invasion at surgery along with completeness of excision are, irrespective of the histological subtype, the best markers of future clinical behaviour. Macroscopic adherence in the mediastinum may be the only sign of capsular penetration—the surgeon should mark it and refrain from incising the capsule to allow full histological assessment.

Medullary and mixed thymoma tend to present at stages I or II, predominantly cortical or cortical more often stage III or IV. However, prognosis is usually 90–100% 5-year survival, patients with myasthenia gravis doing worse than those without. Treatment is surgical supplemented by radiotherapy if there is any possibility of residual tumour or local recurrence (2–10% of cases, more usually the predominantly cortical and cortical types). Distant metastases may need chemotherapy. Well-differentiated thymic carcinoma has an 80% 5-year survival. Thymic carcinoma may require a combination of surgery, radiotherapy and chemotherapy for bulky local disease or distant spread. Disease course relates to tumour type being either aggressive (death in 6 months to 2 years in non-keratinizing carcinoma, sarcomatoid/clear cell/undifferentiated carcinomas), intermediate (squamous cell carcinoma, carcinoid tumour) or indolent (mucoepidermoid/basaloid carcinomas).

Skin Cancer

- Non-Melanocytic Skin Carcinoma
- Malignant Melanoma

20
Non-Melanocytic Skin Carcinoma

1. GROSS DESCRIPTION

Specimen

— smear cytology/curettage/shave biopsy/punch biopsy/incision biopsy/excision biopsy/Mohs' surgery.
— size: length × width × depth (mm).
— curettage, shave and punch biopsies are often small, processed intact and embedded in toto. Slightly larger shaves and punches may be bisected and similarly all processed. In general, margins are not marked and this is also so for incision biopsies which are for diagnostic purposes from the edge of a larger lesion. Histological levels are usually examined. Excisional biopsies attempt to remove the lesion with clear margins of normal skin. Assessment is aided by painting the deep and lateral limits and use of quadrant blocks or serial transverse slices tailored to local protocols. Thus, cases are handled individually according to the specimen size, type of lesion and its size and position within the specimen. If initial histological sections fail to reveal a tumour when an experienced dermatologist has given a strong clinical suspicion that there is one present, the pathologist must always be prepared to carry out further levels for examination. Additional histological clues can be evident, e.g. epidermal dysplasia, dermal inflammation/hyalinization or retraction artefact that would suggest the possibility of an adjacent carcinoma. This is particularly so for recurrences which can be small and difficult to demonstrate. Tumours arising in the face and around the eyes and ears are more difficult to treat with a higher incidence of local recurrence and metastasis. A more complex dermatological surgical technique may be required with peroperative frozen section checking of circumferential surgical margins and wound reconstruction (Moh's micrographic surgery). Sometimes primary or secondary excision specimens are submitted with a central circular deficiency due to prior sampling for research by the clinician. Care must be taken in orientation of the specimen and accurate assessment of tumour diameter and margin distances can be somewhat problematic.

Tumour

Site
— anatomical site: limbs/trunk/head/neck/perineum/epidermal/dermal/subcutaneous.

Size
— length × width × depth (mm) or maximum dimension (mm).

Appearance
— verrucous/warty/nodular/exophytic/sessile/ulcerated/invaginated/cystic/plaque/haemorrhagic/necrotic.

Edge
— circumscribed/irregular.

2. HISTOLOGICAL TYPE

Actinic keratosis, Bowen's disease, squamous cell carcinoma and basal cell carcinoma are the commonest solar-induced non-melanocytic tumours, other skin malignancy being relatively unusual. They arise either as red, scaly patches or as nodular lesions on the sun-exposed head and neck areas of fair-skinned people. A minority are associated with genetic disorders or areas of chronic scarring.

Squamous cell carcinoma
— keratinizing/non-keratinizing.
— 80% are well differentiated and keratinizing.
— variants with adverse prognosis:
    acantholytic (pseudoglandular or adenoid)
    spindle cell (sarcomatoid)
    pseudoangiosarcomatous (pseudovascular)
    small cell or basaloid
    post traumatic (e.g. Marjolin's ulcer)
    adenosquamous (mixed differentiation).
— others:
    verrucous: high rate of local recurrence on the sole of foot and at the anal margin. Locally invasive, exophytic with "church spire" hyperkeratosis and a pushing deep margin of cytologically bland bullous processes
    clear cell (elderly, scalp)
    papillary
    lymphoepithelial
    keratoacanthoma: rapid growth and crateriform with a central keratin plug and lipped rim of hyperplastic squamous epithelium. Difficult to distinguish from and regarded by some as a well-differentiated variant of squamous carcinoma.

Basal cell carcinoma

— the commonest non-melanocytic cutaneous carcinoma characterized by local tissue infiltration, destruction and recurrence and, rarely, metastasis. Circumscribed, local or expansile tumours* have a low risk of recurrence but there is a high risk for those with a diffuse, multifocal or infiltrative growth pattern†. Note that there is often more than one growth pattern in any given lesion.
— nodular*: the commonest subtype with nodules of varying size, ± tumour necrosis and cystic spaces (nodulocystic), peripheral palisading, mitoses and dermal retraction artefact. Includes adenoid (trabecular/ribbons of cells), keratotic (horn cysts, squamous metaplasia), pigmented, fibroepithelial (Pinkus tumour) variants, and those with adnexal (follicular or eccrine) differentiation.
— superficial multifocal†: multifocal nests of tumour budding off the epidermal or hair follicle basal layer. Recurrent due to inadequate primary excision.
— infiltrative and morphoeic‡: small, irregular infiltrating groups in a fibrous or hyaline scirrhous stroma in a poorly circumscribed lesion.
— micronodular‡: multiple small round nests less than 25 cells in diameter, with an asymmetrical, infiltrative growth pattern.
— metatypical/basosquamous carcinoma‡: configuration of a basal cell carcinoma but with more nuclear atypia, a fibroblastic response and foci of malignant squamous differentiation. An intermediate tumour between basal and squamous carcinomas of usual type.

Adnexal carcinoma

— these are rare tumours best dealt with by a pathologist with dermatopathological expertise in the context of a multidisciplinary meeting. Diagnostic clues are cellular atypia, necrosis, mitoses, perineural/lymphovascular invasion and an unusually deep infiltrative margin.
— hair follicle differentiation: tricholemmocarcinoma, malignant pilomatrixoma.
— sebaceous differentiation: epithelioma/carcinoma.
— ductal differentiation: apocrine; eccrine including syringomatous carcinoma, microcystic adnexal carcinoma, malignant chondroid syringoma/nodular hidradenoma/spiradenoma subtypes, porocarcinoma, mucinous carcinoma, aggressive digital papillary adenoma/adenocarcinoma and adenoid cystic carcinoma.

Paget's disease

— extramammary sites are vulva, perineum, scrotum, axillae: see Chapters 7 and 27.

Neuroendocrine carcinoma: Merkel cell or small cell neuroendocrine carcinoma of skin

— head/neck, extremities, elderly.
— chromogranin/synaptophysin/CD56 positive, paranuclear dot CAM5.2/cytokeratin 20 positive.
— ± overlying basal or squamous carcinoma (in situ or invasive).
— clinically exclude secondary small cell carcinoma of lung (CK20 negative/TTF-1 positive).
— poor prognosis, local recurrence and nodal metastases are common. Treatment is primary excision with wide margins. Adverse indicators are size >2 cm, mitoses >10/10 hpfs, extensive lymphovascular invasion or positive primary excision margins.

Dermal tumours

— fibrohistiocytic, neural, muscular, vascular, adipose.

Leukaemia

— 5–10% of leukaemia cases: sometimes as a first manifestation of disease but more often secondary to widespread systemic or recurrent disease.
— children: acute lymphoblastic leukaemia (ALL) (CD79a, CD10 (CALLA) positive ± tdt, Ki-67 > 90%).
— adults: chronic lymphocytic leukaemia (CLL) (CD5, CD23) or CML (CD68/chloroactetate esterase/myeloperoxidase). Also multiple myeloma (CD79a, CD138, κ, λ light chain restriction, Bence–Jones proteinuria, monoclonal gammopathy, lytic skull lesions).

Lymphoma: primary

— disease confined to skin for at least 6 months after complete clinicopathological staging.
— T cell 65%: B cell 25%.

T cell, indolent behaviour:

mycosis fungoides (MF) ± follicular mucinosis: MF has overlapping patch, plaque, tumour, erythrodermic and poikilodermic stages
Pagetoid reticulosis: intraepidermal T cell infiltrate
granulomatous slack skin disease: T cell infiltrate with giant cell elastophagocytosis
anaplastic large cell, CD30 positive: >30% of the cells are blasts and >75% of these are CD30 positive. Usually T cell, sometimes null
small/medium cell: <30% CD30 positive blasts in the infiltrate
lymphomatoid papulosis: recurring self-healing papulonodular eruption of uncertain malignant potential with variable polymorphous/monomorphous pictures including CD30 positive large cells.

T cell, aggressive behaviour:

Sézary syndrome: the leukaemic phase of erythrodermic cutaneous T-cell lymphoma
anaplastic large cell, CD30 negative

pleomorphic medium/large cell
subcutaneous panniculitis-like lymphoma
NK, NK/T cell: CD56 positive, occasionally T-cell positive and angiocentric/destructive.

B cell, indolent behaviour:

follicle centre lymphoma: head and neck (scalp). CD20/CD10/bcl-6. Widely spaced follicles in deep dermis and subcutaneous fat. Includes good prognosis large cell variant
marginal zone lymphoma (good prognosis—a minority have Borrelia burgdorferi organism as a chronic antigenic stimulus). Nodular perivascular/periadenexal or diffuse infiltrate of centrocytoid/monocytoid cells including reactive germinal centres. Lymphoplasmacytoid forms, rare lymphoepithelial lesions. Trunk, head and neck, upper limbs.

B cell, intermediate behaviour:

mantle cell lymphoma (rare: exclude spread from systemic disease)
large cell lymphoma of the lower legs in elderly women: grenz zone, dermal/subcutaneous, perivascular/periadnexal infiltrate. CD20/CD10/bcl-6. Variable 5-year survival 58–95%. Multiplicity of lesions is adverse.

B cell, aggressive behaviour:

large cell lymphoma in other clinical settings, e.g. intravascular large B-cell lymphoma (angiotrophic lymphoma)
lymphoblastic lymphoma in children and adults—tdt positive.

The behaviour of lymphomatoid granulomatosis (EBV positive large B cells, with reactive small T cells) depends on the content of blasts, grade 3 equating to diffuse large B-cell lymphoma.

Lymphoma: secondary
— secondary to nodal/systemic disease.

For details on the classification, immunophenotyping and staging of lymphoma, refer to Chapter 35.

Metastatic carcinoma
— kidney, breast, gut, lung, oral cavity, ovary, malignant melanoma.
— single/multiple nodule(s) commonly on the trunk and head and neck regions, sometimes in the vicinity of the primary lesion.
— some metastases can be epidermotropic and simulate a primary lesion.
— secondary small cell carcinoma of lung or gut carcinoid can mimic Merkel cell tumour.

3. DIFFERENTIATION
Well/moderate/poor/undifferentiated, or Grade 1/2/3/4.
— basal cell carcinomas are usually not graded but subtyped with comment made on any unusual differentiation features, e.g. metatypical.

— for squamous carcinoma based on cellular atypia, keratinization and intercellular bridges. Broder grade I (>75% differentiated), II (25–75%), III (<25%) and IV (no differentiation).
— for adnexal carcinoma based on the degree of appendage differentiation, atypia, mitoses and necrosis.
— undifferentiated carcinomas are grade 4.

4. EXTENT OF LOCAL TUMOUR SPREAD

Border: pushing/infiltrative.
Lymphocytic reaction: prominent/sparse.
The TNM classification applies to any skin carcinoma, but not carcinomas of the eyelid, vulva and penis.

pTis carcinoma in situ
pT1 tumour ≤2 cm in greatest dimension
pT2 tumour >2 cm but ≤5 cm in greatest dimension
pT3 tumour >5 cm in greatest dimension
pT4 tumour invades deep extradermal structures (cartilage, skeletal muscle, bone)
optional descriptors for pT1–3 are:
a. limited to dermis or ≤2 mm in thickness
b. limited to dermis and >2 mm in thickness but ≤6 mm
c. invading subcutis and/or >6 mm in thickness
pT4:
a. ≤6 mm
b. >6 mm.

Depth of dermal invasion for squamous carcinoma can also be expressed in anatomical Clark level I–V (see Chapter 21). High-risk types correspond to Clark levels IV and V (reticular dermis, subcutaneous fat).

5. LYMPHOVASCULAR INVASION

Present/absent.
Intra-/extratumoral.

— not commonly seen but when present correlates with recurrence and metastases.

6. LYMPH NODES

Site/number/size/number involved/limit node/extracapsular spread.
Regional nodes: those appropriate to the site of the primary tumour. Although not usually submitted, a regional lymphadenectomy will ordinarily include a minimum of six lymph nodes. Involvement of iliac, pelvic, abdominal or intrathoracic nodes is classified as pM1.

pN0 no regional lymph node metastasis
pN1 metastasis in regional lymph node(s).

7. EXCISION MARGINS

Distances (mm) to the nearest painted deep and peripheral excision margins, either of quadrant blocks or serial transverse slices (toast

racked). Comment should also be made on the presence of dysplasia or in-situ change at the margins.
Adequate treatment is based on successful complete primary excision or, if there is initial margin involvement, on secondary re-excision. Involved is tumour at (=0 mm) a margin; close to ≤1 mm.

8. OTHER PATHOLOGY
Squamous cell carcinoma is more prone to lymph node metastases particularly if >2 cm diameter or >2 mm in thickness, poorly differentiated or with perineural spread. Morphologically it shows nuclear stratification, intercellular bridges ± keratinization. General prognostic indicators for squamous carcinoma are stage, level of dermal invasion and tumour thickness. Recurrent tumours tend to be ≥4 mm thick with involvement of the deep dermis and fatal tumours at least 1 cm thick with extension into subcutaneous fat.
Predisposing lesions to cutaneous carcinoma are:

— actinic keratosis/solar elastosis; sun exposure.
— Psoralen plus ultraviolet A (PUVA) treatment for psoriasis.
— varicose ulcers, lichen planus, hidradenitis suppurativa.
— immunosuppression post transplant, HIV.
— Bowen's disease—indolent progression to carcinoma.
— condyloma accuminatum, Bowenoid papulosis, human papillomavirus (HPV) infection—perineum/perianal margin squamous carcinoma.
— epidermodysplasia verruciformis, xeroderma pigmentosum.
— naevus sebaceous of Jadassohn.
— naevoid basal cell carcinoma syndrome.

Double pathology may be encountered, e.g. basal or squamous cell carcinoma overlying Merkel cell tumour, basal cell carcinoma and syringocystadenoma papilliferum in naevus sebaceous of Jadassohn, basal cell carcinoma and dermatofibroma.

Pseudoepitheliomatous (pseudocarcinomatous) hyperplasia may be seen in association with: chronic venous stasis, ulceration, chronic inflammation, e.g. pyoderma gangrenosum, and overlying neoplasms, e.g. granular cell tumour.

Distinction between actinic keratosis, carcinoma in situ and invasive squamous carcinoma can be difficult and some of these lesions should be designated "best regarded as squamous carcinoma". Treatment (primary surgical excision ± radiotherapy) is the same for both.

Sebaceous carcinoma may be periocular and aggressive or extraocular and non-aggressive. It forms a spectrum of behaviour with sebaceous epithelioma (local recurrence).

Skin carcinoma varies greatly in its immunophenotypic expression.

Immunophenotype
Squamous cell carcinoma: high-molecular-weight cytokeratins, AE1/AE3, CK5/6, EMA, CEA positive; BerEP4 negative.

Basal cell carcinoma: low-molecular-weight cytokeratins, BerEP4 positive; EMA, CEA negative.

Adnexal carcinomas: usually EMA and CEA positive, and differential molecular weight cytokeratin expression according to their differentiation. Generally, CAM5.2 (low molecular weight) and AE1 (intermediate molecular weight) positive.

Some centres use smear cytology with immediate reporting to distinguish basal cell from non-basal cell cutaneous carcinoma to facilitate a one-stop assessment and institution of treatment.

9. OTHER MALIGNANCY

Sarcoma

Dermal and subcutaneous soft tissue tumours may have classical clinical features, e.g. angiosarcoma of the scalp in the elderly and Kaposi's sarcoma in AIDS. However, they are classified according to their cell of origin and malignancy is assessed by cellularity, cellular atypia, mitotic activity and infiltrative margins. Immunocytochemistry is often very useful in determining histogenesis, e.g. desmin, h-caldesmon, actin (muscular), S100 (neural, melanocytic (also HMB-45, melan-A), chondroid, adipose), CD31, CD34, factor VIII (vascular), CD68 ((fibro-)histiocytic) and CD34 (dermatofibrosarcoma). Examples are: cutaneous leiomyosarcoma, dermatofibrosarcoma protuberans, angiosarcoma, epithelioid haemangioendothelioma, malignant nerve sheath tumour, liposarcoma and extraskeletal myxoid chondrosarcoma (usually extending from deep soft tissues).

Kaposi's sarcoma is found in the elderly (solitary) or young (AIDS, multiple). The early patch/plaque phase is subtle, characterized by linear "vascular" slit-like spaces in the dermal collagen oriented parallel to the epidermis. Later there is a sieve-like pattern with extravasation of red blood cells and spindle cell proliferation. Associated with HHV-8.

Immunocytochemistry is also important in the differential diagnosis of cutaneous spindle cell lesions, viz. spindle cell squamous carcinoma vs. malignant melanoma, leiomyosarcoma, metastatic sarcoma and atypical fibroxanthoma. A working panel is CAM5.2, AE1/AE3, S100, melan-A, desmin, h-caldesmon, smooth muscle actin, CD68 and alpha-1-antitrypsin. Other morphological clues are dysplasia of the surface squamous epithelium (carcinoma), junctional activity and melanin pigmentation (melanoma), Touton-like giant cells (AFX) and eosinophilic fusiform spindle cells (leiomyosarcoma). Clinical history is important to exclude a metastasis.

A further indication for immunohistochemistry is in the distinction between Merkel cell tumour (CK20/synaptophysin/CD56/EMA ± CD99), lymphoma (CD45 (lymphoblastic—tdt/CD99)), PNETs (CD99 ± NSE/neurofilament) and small cell malignant melanoma (S100/HMB-45/melan-A).

Lymphoma

Immunocytochemistry (for cell lineage and light chain restriction) and molecular studies (T-cell receptor gene and immunoglobulin heavy chain gene rearrangements) are also of use in cutaneous lymphoma. T-cell lymphomas show epidermotropism while B-cell lymphomas often have a dermal grenz zone and a "bottom-heavy" infiltrate extending into the subcutis. Note that the latter can also show reactive germinal centres and a polymorphous reactive cellular infiltrate. Low-grade T-cell lymphomas have a horizontal band-like dermal growth pattern while high-grade lesions and B-cell lymphomas are sharply demarcated with a nodular, vertical and three-dimensional growth. Molecular studies are particularly helpful in inflammatory conditions simulating cutaneous lymphoma, e.g. lymphocytoma cutis and lymphomatoid reactions to drugs and insect bites. Designation of lymphoma can sometimes be difficult and should always be clinicopathological in the context of a multidisciplinarian meeting. In some cases the subsequent clinical progression or lack of it is the final arbiter.

21
Malignant Melanoma

1. GROSS DESCRIPTION

Specimen

— curettage/shave biopsy/punch biopsy/incision biopsy/excision biopsy.
— size: length × width × depth (mm).
— any recent change in a melanocytic lesion such as irregularity of profile, border or pigmentation should be assessed by a dermatologist and regarded with suspicion. Diathermy and curettage are avoided as this distorts histological detail. Rather, primary cold knife excision with clear (at least 2 mm) margins should be attained for initial histological designation, which will usually require examination through multiple levels. The deep and lateral margins are painted prior to blocking into quadrant or serial transverse slices. Some pathologists will either photograph the surface or take a face-down photocopier image for a record of its outline or proximity to a margin. Re-excision specimens usually have a central longitudinal scar and quadrant blocks with a double central transverse slice will generally suffice. With increasing sun exposure and public awareness malignant melanoma, "early" and borderline lesions, e.g. melanoma in situ and dysplastic naevus, have increased in incidence.

Tumour

Site

— anatomical location—trunk, limbs, head/neck, perineum, mucosal, ocular, multifocal (1–5%).
— epidermal/dermal/subcutaneous.

Size

— length × width × depth (mm) or maximum dimension (mm).

Appearance

— verrucous/nodular/sessile/ulcerated/pigmented or non-pigmented/halo/satellite lesions/scarring.

Edge

— circumscribed/irregular.

2. HISTOLOGICAL TYPE

Malignant melanoma in situ

— intraepidermal: spread can be lentiginous (continuous basal layer) or upward (single cells, nests, "buck-shot" or Pagetoid) in this non-invasive radial growth phase.

Lentigo maligna melanoma

— face/Hutchinson's melanotic freckle: a lentiginous single and nested basal layer proliferation of melanocytes with cytological atypia (enlarged, hyperchromatic angular nuclei and cytoplasmic vacuolation) ± architectural atypia (expanded junctional nests) on a background of dermal solar elastosis. Expansion and spindling of junctional nests and any clinically nodular areas should raise a suspicion of invasion. The clinical term lentigo maligna encompasses any degree of proliferation that is confined to the epidermis (i.e. it includes Clark level I or melanoma in situ), while lentigo maligna melanoma implies the presence of dermal invasion (at least Clark level II).

Superficial spreading melanoma

— radial phase of spread.[1]

Usually an asymmetrical lateral border of atypical junctional cell nests with a central segment of epidermis showing upward melanocytic spread (single cells/nests/"buck-shot" patterns). Moderate dusty pigmentation ± a dermal component related to the growth phase.

Nodular melanoma

— vertical phase of spread.[2]

Often exophytic/nodular and thick ± pigmentation, with ≤2 or 3 rete pegs showing atypical junctional nests at the lateral border of the lesion.

Acral/mucosal/lentiginous melanoma

— sole of foot, nail bed, mucosae. Features are often a combination of lentigo maligna and superficial spreading patterns ± a nodular, vertical growth phase component.

[1]Radial growth phase includes melanoma in situ (i.e. intraepidermal) ± microinvasion of the papillary dermis. The radial phase may be indolent with no metastatic potential and 95–100% survival rate. The dermal component is usually <1 mm thick, i.e. the lesion is wider than it is deep and can have morphologically bland cell nests (usually <10 cells across) of uniform size and cytological appearance. This may be accompanied by signs of regression with a brisk lymphocytic response. The radial phase potentially progresses by clonal expansion to the vertical phase.

[2]Vertical growth phase tumour comprises expansive nests, nodules or plaques of cytologically atypical melanoma cells in the dermis; it implies a biological potential for metastatic spread and is the main determinant of prognosis. The cell nests are usually larger than the biggest intraepidermal nest, ≥10–25 cells in dimension, show variation throughout the lesion, mitoses and a variable host dermal lymphocytic response. Vertical growth phase melanomas are often at least Clark level III and thicker than 1 mm with an inconstant relationship between the width and depth of the lesion.

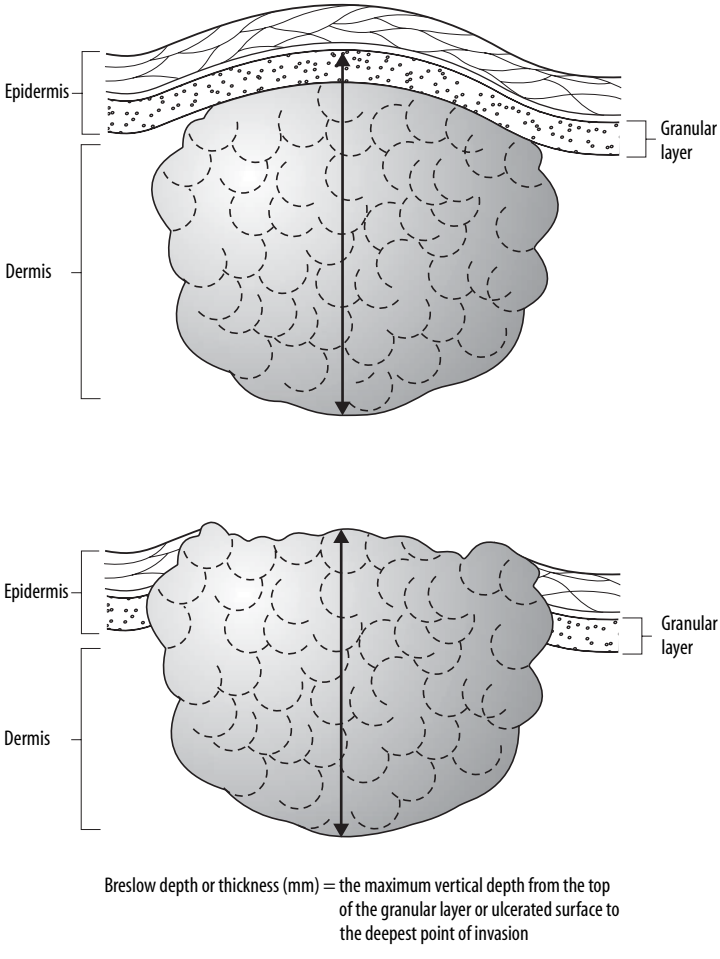


FIGURE 21.1. Malignant melanoma.

In general, these main subtypes do not show prognostic differences but there is correlation with recurrence and metastases, e.g. nodular melanoma is often thick (with a significant Breslow depth) and ulcerated. Knowledge of the various clinicopathological subtypes also helps in their diagnostic recognition.

Others

— e.g. desmoplastic, neurotropic, verrucous, balloon cell, signet ring cell, small cell, myxoid, minimal deviation, metastatic, malignant blue naevi.

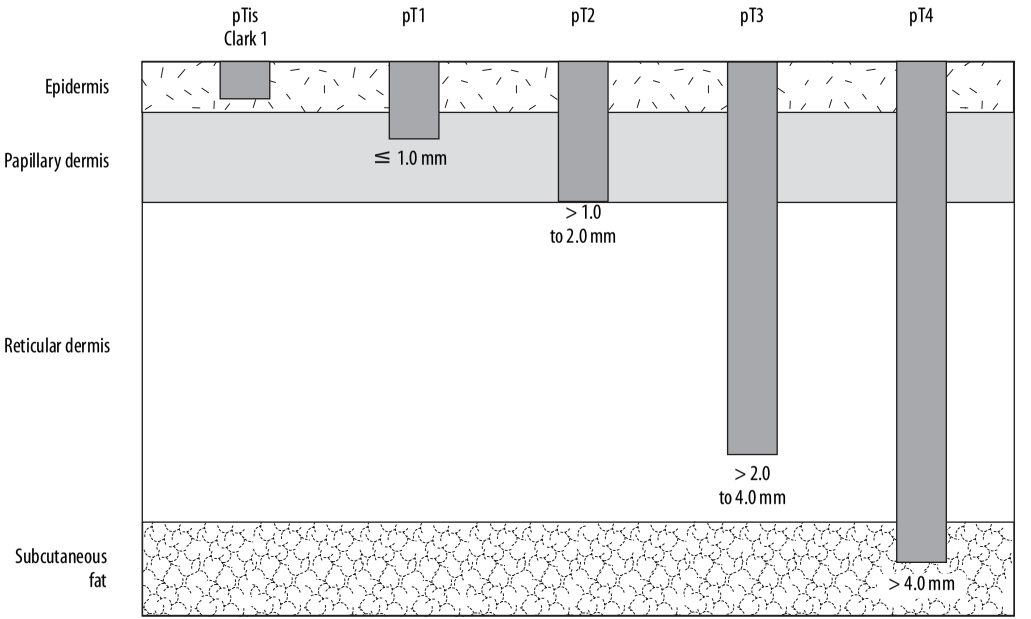


FIGURE 21.2. Malignant melanoma.

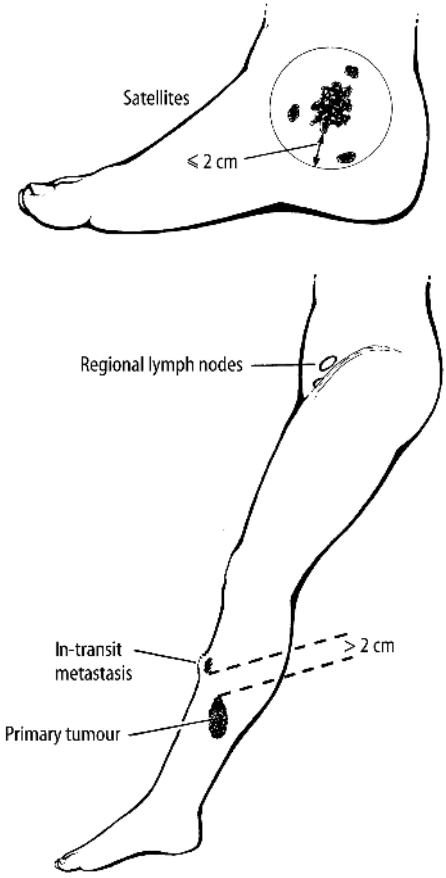


FIGURE 21.3, 21.4. Malignant melanoma.

3. DIFFERENTIATION/CELL TYPE

— epithelioid.
— spindle cell.
— mixed.

4. EXTENT OF LOCAL TUMOUR SPREAD

Border: pushing/infiltrative.
Lymphocytic reaction: prominent/sparse/absent—the number of tumour-infiltrating lymphocytes has a positive association with survival.
Paradoxically, in thin melanomas >75% lesional regression (full thickness destruction of melanoma cells, lymphohistiocytic infiltrate, fibrosis, melanophages, vascular ectasia) is an adverse prognostic factor. It is also

regarded by some as an explanation for an occult cutaneous primary in the presence of widespread metastatic disease.

The TMN classification applies to malignant melanoma of skin at all sites including eyelid, vulva, penis and scrotum, but not those arising in mucous membranes (oral cavity, nasopharynx, vagina, urethra, anal canal), conjunctiva or uvea. Visceral melanomas do not have a separate classification.

The TNM classification of malignant melanoma incorporates three main prognostic features: tumour thickness, anatomical Clark levels (in pT1 category only) and the absence or presence of ulceration (defined as the histological absence of an intact epidermis overlying a major portion of the primary melanoma).

Breslow depth or thickness (mm)

— eyepiece graticule measurement of tumour maximum vertical diameter from the top of the granular layer or ulcerated tumour surface to the deepest point of invasion. Melanoma cells in adjacent pilosebaceous unit epithelium do not count. S100 or melan-A immunostains can help highlight melanoma cells in the dermis that might otherwise be obscured by a heavy lymphocytic infiltrate at the base of the lesion.

Anatomical Clark level

— increasing levels of invasion are associated with decreased survival, although it may simply reflect thickness of the lesion.

I	intraepithelial
II	papillary dermis
III	papillary–reticular interface: papillary dermis filled and expanded down to an interface marked by the position of the superficial vascular plexus
IV	reticular dermis
V	subcutaneous fat.

pTis	melanoma in situ (Clark level I)/severe melanocytic dysplasia
pT1	tumour ≤ 1 mm in thickness
	a. Clark level II or III, without ulceration
	b. Clark level IV or V, or, with ulceration
pT2	1 mm < tumour ≤ 2 mm in thickness
	a. without ulceration
	b. with ulceration
pT3	2 mm < tumour ≤ 4 mm in thickness
	a. without ulceration
	b. with ulceration
pT4	tumour > 4 mm in thickness
	a. without ulceration
	b. with ulceration.

Note that ulceration (particularly if >3 mm) is an adverse independent prognostic factor—50% 10-year survival vs. 78% if non-ulcerated. It can also result in understaging of Breslow thickness although there is a strong correlation between them.

Definition: MIN (melanocytic intraepithelial neoplasia)
= melanocytic dysplasia and melanoma in-situ (level I) pTis.

Levels are examined to exclude any associated microinvasion (single cells, small groups of cell in the papillary dermis).

5. LYMPHOVASCULAR INVASION

Present/absent.
Intra-/extratumoral.
Rarely seen, but perineural invasion is commonly present in neurotropic and desmoplastic melanomas with a subsequent high recurrence rate.

6. LYMPH NODES

Site/number/size/number involved/limit node/extracapsular spread.
Regional nodes: those appropriate to the site of the primary tumour. A regional lymphadenectomy will ordinarily include a minimum of six lymph nodes. Classification based on sentinel node biopsy alone is designated (sn), e.g. pN0 (sn).

pN0 no regional lymph node metastasis
pN1 metastasis in one regional lymph node
  a. micrometastasis (clinically occult)
  b. macrometastasis: detected clinically with confirmation after lymphadenectomy, or, gross extracapsular invasion
pN2 metastasis in 2–3 regional lymph nodes
  a. micrometastasis
  b. macrometastasis
  c. in-transit metastases/satellite(s) without metastatic lymph nodes
pN3 4 or more metastatic lymph nodes, or matted lymph nodes, or in-transit metastases/satellite(s) plus metastatic lymph node(s).

Satellites are tumour nests or nodules (macro- or microscopic (>0.05 mm)) within 2 cm of the primary tumour but not contiguous with it and are prognostically adverse. Levels are recommended to demonstrate lack of continuity. In-transit metastases involve skin or subcutaneous tissue more than 2 cm from the primary tumour but not beyond the regional lymph nodes.

Spread of malignant melanoma is to regional nodes, skin (satellite nodules and in-transit metastases), liver, lungs, gastrointestinal tract, bone and CNS.

pM1a skin, subcutaneous tissue or lymph node(s) beyond the regional nodes
pM1b lung
pM1c other sites, or any site with elevated serum lactic dehydrogenase (LDH).

7. EXCISION MARGINS

Distances (mm) to the nearest painted deep and peripheral excision margins either of quadrant blocks if specimen size allows or serial slices

(toast racked)—of the vertical and radial disease phases and any in-situ change.

Minimum recommended margins of clearance vary according to the tumour depth of invasion:

Depth	Minimum margin
<0.76 mm	5 mm
0.76–2 mm	10 mm
>2 mm	20 mm

Adequate treatment is based on successful complete primary excision or, if there is initial margin involvement, secondary re-excision. This is supplemented by regional node dissection and systemic therapy for metastatic disease. Sentinel lymph node biopsy may be used in patients with clinically negative regional lymph nodes and a vertical growth phase malignant melanoma ≥ 1 mm thick. It involves serially slicing the node with preparation of multiple haematoxylin and eosin (H&E) and matching immunohistochemical stains for S100 and HMB-45. Differential diagnoses include sinus histiocytes, capsular naevus cell nests and benign ductal epithelial inclusions. If positive, a regional lymphadenectomy is carried out.

8. OTHER PATHOLOGY

— pigmentation: none/light/moderate/heavy.
— mitoses: number/10 hpfs (×40 objective) or absent, low (<6/mm^2) or high.
— ulceration: present/absent.
— elastosis: present/absent.
— regression: present / absent — inflammation / fibrosis / telangiectasia / melanophages.
— pre-existing lesion: present/absent and less common than de-novo melanoma.
— satellite lesions: present/absent; distance (mm) from primary.

Primary vs. secondary/recurrence: secondary tumour tends to be nodular and dermal/subcutaneous ± vascular invasion with no epidermal component. Occasionally secondary melanoma may show epidermal changes but usually the dermal disease is more extensive in width. Some melanomas can develop multiple locoregional cutaneous recurrences over many years and do not develop metastatic disease, although such satellite nodule and in-transit metastases are an indicator of potential systemic dissemination. They are regarded as tumour emboli arrested in lymphatics which then grow to form a tumour mass. They are seen in about 5% of malignant melanomas >1 mm thick.

Immunophenotype

— useful in the distinction between melanoma and non-melanocytic tumours but not reliable for separating benign and malignant melanocytic lesions. Note also that some melanomas are cytokeratin (CAM5.2), CEA and EMA positive.

— S100 protein, HMB-45 and melan-A.
— Masson Fontana for pigment.
— Ki-67 proliferation index and p53: increased in malignant melanocytic lesions.

Dysplastic naevus: variable reports of sporadic and familial predisposition to malignant melanoma. Strict criteria (clinical and pathological) must be adhered to (see below) as there is a range of benign naevi with active junctional components that can mimic dysplastic naevus or melanoma, e.g. junctional/pagetoid Spitz naevus, pigmented spindle cell naevus, halo naevus, traumatized and irradiated naevus, acral and genital naevi. Age, anatomical site, lesion type and clinical history must all be considered along with the morphology.

— single or multiple (dysplastic naevus syndrome).
— ≥4 mm with variable pigmentation and irregular borders.
— nested and lentiginous melanocytic proliferation.
— architectural and cytological atypia.
— elongation/lateral fusion of rete pegs.
— dermal lamellar fibroplasia with vascularization and chronic inflammation in the dermis.

Morphological clues to a diagnosis of malignant melanoma are: lesion asymmetry, extension of atypical melanocytes up into the epidermis and lateral to the lesion, melanocytic atypia and lack of dermal maturation, deeply placed mitoses and a dermal lymphocytic infiltrate. Melanocytic cell nests also vary in size, shape and cytological atypia within a lesion.

Prognosis

Prognosis of melanoma is unpredictable but relates strongly to the vertical component or thickness/depth of invasion and adequacy of excision with the width of margins tailored accordingly. Estimated overall 5-year survival rates are about 60% but tumour stage/thickness is the most powerful prognostic determinant:

	5-year disease-free survival	Regional metastases at 3 years
<0.76 mm	>95%	0%
>1.5 mm	40–60%	50–60%

Prognostically, melanomas can therefore be regarded as being thin (<0.76 mm), intermediate (0.76–1.5 mm) or thick (>1.5 mm).

Other adverse indicators are patient age (>50 years), sex (male), histological regression, histological type (nodular), vascular invasion, tumour phase (vertical), satellitosis, necrosis, ulceration, mitotic activity and anatomical site (sole of foot, head, neck and back are worse). One study found that a prognostic index of tumour thickness multiplied by the number of mitoses/mm^2 was the most accurate method of predicting patients who would remain disease free. Occasionally malignant melanoma may present as metastatic disease, e.g. axillary nodes due to complete regression of a cutaneous lesion leaving no obvious primary

tumour on examination. Other possible occult sources are the eye and mucosal surfaces of the oesophagus, vagina and anal canal. These mucosal, acral lentiginous and subungal melanomas have poor prognosis due to late presentation. In general, factors such as age, pregnancy, lesion diameter, histological type and inflammatory infiltrate are outweighed by tumour thickness and stage. However, even in thick (>5 mm) melanomas there is a subset of patients who may survive 10 years or more. Their tumours tend to be of spindle cell or Spitz-like cell type with a lack of mitoses and vascular invasion. Conversely, occasional thin melanomas can metastasize.

Balloon cell malignant melanoma tends to develop multiple cutaneous and subcutaneous metastases. The inter-related desmoplastic (myofibroblastic differentiation) and neurotropic (Schwann cell differentiation) variants arise mostly on the head and neck of elderly patients (particularly the lip) and show a high incidence of recurrence and metastases. Diagnosis requires an index of suspicion to distinguish from a dermal scar, recognition of tumour infiltrate in the deep dermis and accompanying clues in the form of an epidermal component. Immunocytochemistry (S100) is important in confirmation, although it may be negative (HMB-45/melan A). Perineural invasion is a feature.

Breast Cancer

- Breast Carcinoma

22
Breast Carcinoma

1. GROSS DESCRIPTION

Specimen

— fine needle aspirate/needle core biopsy/localization biopsy/open biopsy/segmental excision/partial mastectomy/mastectomy. Optimal fixation is important in assessing tumour type, grade, lymphovascular invasion and hormone receptor expression.
— axillary nodes: sentinel biopsy/sampling/clearance.
— size (cm) and weight (g).
— symptomatic breast cancer usually presents with a palpable lump, skin tethering, nipple rash (Paget's disease)/retraction or discharge. Asymptomatic in-situ or invasive lesions are detected at two-view mammography (80–90% sensitivity) as either linear branching microcalcifications, a discrete mass or an area of stromal distortion and spiculate density. Mammographic screening is detecting a higher yield of smaller invasive cancers and "earlier" lesions with a greater proportion of in-situ carcinoma than in the symptomatic population.
— localization biopsies should be accompanied by a post-operative specimen X-ray and have attached orientation sutures/clips in place according to a pre-agreed protocol ± an in-situ guide wire(s). Breast-conserving surgery by wide local excision removes the tumour with a 1-cm rim of normal tissue or a more extensive cylindrical (superficial to deep) excision (segmentectomy/quadrantectomy). Partial mastectomy involves removal of the tumour and surrounding breast with an overlying ellipse of non-nipple bearing skin. Again, orientation sutures are attached allowing differential painting of surgical margins. Mastectomy removes the breast tissue and overlying skin including the nipple with the chest wall left intact. A subcutaneous mastectomy leaves the skin intact for reconstructive procedures but removes the breast tissue and nipple–areolar complex. The axillary fat and contents may be submitted in continuity, or separately as either a sampling or more usually a multipart clearance procedure. Needle core biopsies are usually 19 gauge providing three or four thin cores of tissue measuring up to 1.5–2 cm long. Gentle painting with alcian blue allows visualization at the paraffin block cutting stage and histological levels are examined until any represented mammographic

abnormality is detected. Specimen X-ray calcifications are usually seen histologically in about 80% of cases and about 50% are due to in-situ or invasive disease.

Male breast carcinoma (1% of cases) occurs in older men, presents late and has a poor prognosis. It shows the same range of morphological characteristics as female breast cancer.

Bilateral cancer occurs in younger women and is more often lobular in type. There is also a definite familial risk with breast cancer, some 20% of which can be attributed to BRCA1 and BRCA2 gene abnormalities with associated ovarian, uterine, urinary tract and colon cancers.

Tumour

Site

— right/left/bilateral.
— quadrant: 50% UOQ, 15% UIQ, 10% LOQ, 17% central, 3% diffuse (massive or multifocal). Breast cancer occurs either as a localised lesion, or, multiple invasive foci not connected by associated DCIS and clearly separated by normal breast tissue. The latter probably arise either from a number of abnormal ductulolobular units or as a result of seeding and spread from involved lymphovascular channels. Bilateral and multifocal disease (10–15%) are more frequently seen in lobular than ductal cancer.
— distances (cm) from the nipple and resection limits.

Size

— maximum dimension of invasive lesion (cm).
— maximum dimension of whole tumour (invasive + ductal carcinoma in situ (DCIS)) (cm).
— microscopic measurement updates and takes precedence over gross measurement. This is particularly so for small and poorly defined cancers, e.g. infiltrating lobular, the latter sometimes requiring specimen mapping and blocking to determine its extent.
— in multifocal carcinoma the largest tumour is used to designate the pT category.
— tumour size in a biopsy with positive margins is added to any residual in the mastectomy specimen to determine pT.

Appearance

— scirrhous/fleshy/mucoid/cystic/diffuse thickening.

Ductal carcinoma tends to form a discrete mass lesion whereas lobular carcinoma can be difficult to define clinically, radiologically, cytologically and at the laboratory dissection bench. This has obvious implications for completeness of excision in patients treated with breast-conserving surgery and the pathological assessment of the surgical margins.

Edge

— circumscribed/irregular.

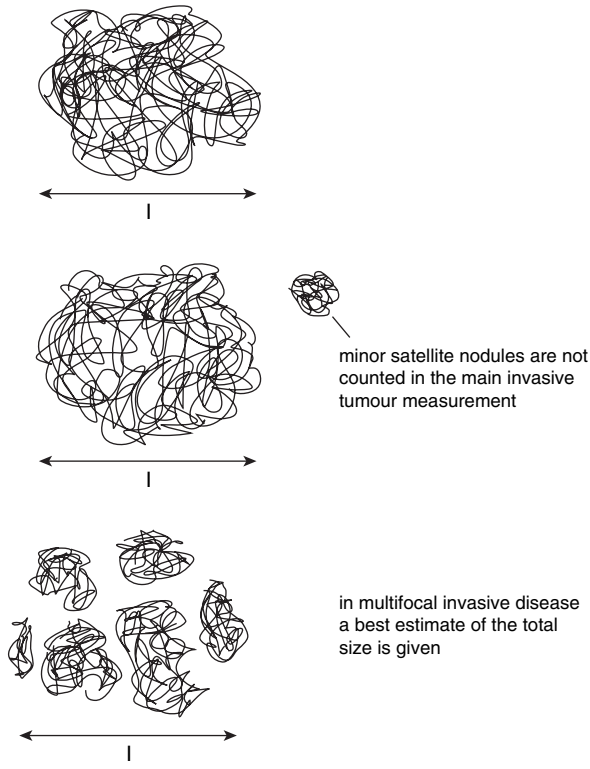


FIGURE 22.1. Breast carcinoma: invasive tumors measurements.

2. HISTOLOGICAL TYPE

In-situ carcinoma

Ductal carcinoma in situ

— bound by basement membrane involving ≥2 ducts or 2–3 mm diameter. Epithelial proliferation of lesser extent is designated atypical ductal hyperplasia unless of high cytological grade or with comedonecrosis.
— nuclear grade: low, intermediate, high.
  • low is monomorphic evenly spaced cells with small central nuclei, few mitoses and necrosis is rare
  • high is pleomorphic irregularly spaced cells with large irregular nuclei, coarse chromatin, ≥1 prominent nucleolus, mitoses and often necrosis. Loss of cell polarization.
— necrosis: comedo or punctate. Comedo = central eosinophilic necrosis containing 5 or more pyknotic nuclei.

— cell polarization: present or absent.
— architectural patterns: comedo
solid
cribriform
papillary
micropapillary.

Rarer forms include encysted papillary, clinging (flat epithelium with low or high grade cytology), signet ring cell, apocrine (rare: needs atypia/necrosis/mitoses), clear cell, cystic hypersecretory and neuroendocrine variants.

Lobular carcinoma in situ
— uniform cells populating the lobule.
— no lumen in the acini.
— ≥50% of the acini in the lobule expanded and filled.
— ± Pagetoid spread into ducts.
— potentially multifocal (70%) and bilateral (30–40%).
— epithelial proliferation of lesser extent (e.g. with preservation of lumina) is designated atypical lobular hyperplasia.

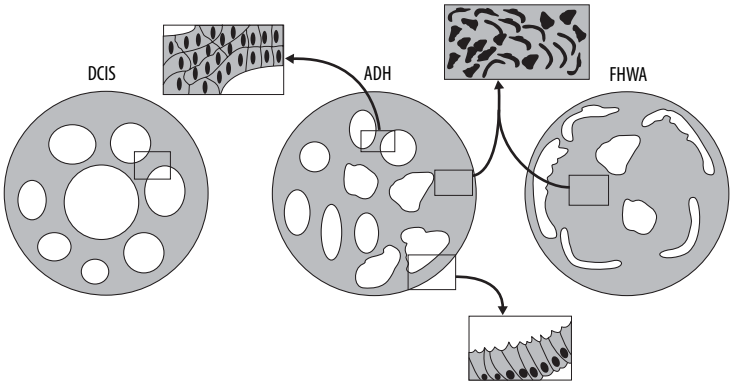


FIGURE 22.2. Ductal carcinoma in-situ (DCIS) versus atypical ductal hyperplasia (ADH) versus florid hyperplasia without atypia (FHWA): cytology and histology. DCIS features smooth, punched-out luminal borders within involved basement-membrane-bound space. The cytological features are regular and present throughout the entire population of at least two basement-membrane-bound spaces. FHWA is the most densely cellular and extensive of the proliferative disease without atypia lesions, also called "papillomatosis". There are ragged, often slit-like luminal borders. The nuclei throughout the involved area show variablity and tendency to a swirling pattern, as illustrated. ADH has features predominantly of non-comedo, cribriform DCIS, but also some features of proliferative disease without atypia or normally polarized cells within the same basement-membrane-bound space. (Page DL, Rogers LW. Combined histologic and cytologic criteria for the diagnosis of mammary atypical ductal hyperplasia. Hum Pathol 1992;23:1095–1097, copyright © 1992, with permission from Elsevier)

Distinction between DCIS and lobular carcinoma in situ (LCIS) is not always easy, e.g. lobular cancerization by low-grade DCIS and, rarely, mixed lesions occur. Loss of E-cadherin expression favours a lobular proliferation.

Microinvasion

— ≤1 mm from the adjacent basement membrane with infiltration of non-specialized interlobular/interductal stroma.
— the presence of multiple foci of microinvasion should be noted, but it is classified according to the largest focus and not the sum total of them.

Minimal invasive cancer

— variably defined as <0.5 cm or <1 cm maximum dimension.

Invasive carcinoma

Ductal

— no specific type (NST): 70–75% of breast cancer.

Lobular

— 15% of breast cancer.
— classical: 40%; single files of small cells/targetoid periductal pattern/AB-PAS positive intracytoplasmic lumina.

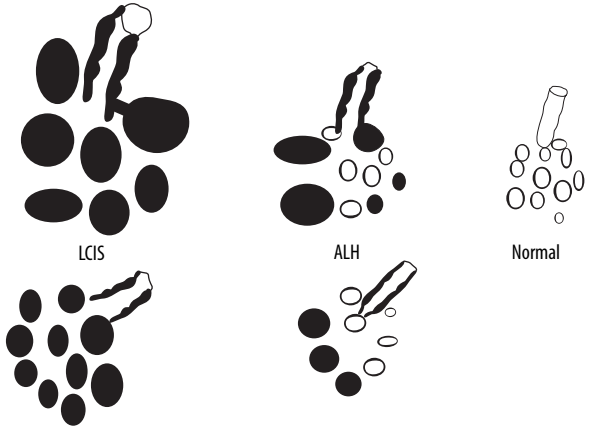


FIGURE 22.3. Schematic demonstration of diagnostic criteria for lobular carcinoma in-situ (LCIS). There is distention and distortion of more than half the acini, and an absence of central lumina. When these changes are less well developed (i.e. <50% of acini involved) atypical lobular hyperplasia (ALH) is diagnosed. Note that the pagetoid spread into adjacent ducts is more common in LCIS, but may be seen in ALH. (Page DL, Kidd TE, Dupont WD, Simpson JF, Rogers LW. Lobular neoplasia of the breast: higher risk for subsequent invasive cancer predicted by more extensive disease. Hum Pathol 1991;22:1232–1239, copyright © 1991, with permission from Elsevier)

— alveolar: nested pattern of 20 or more cells.
— solid: sheets.
— trabecular: bands of cells two to four across.
— signet ring cell.
— pleomorphic: classical pattern but with cytological atypia.
— mixed: 40%; more than one component of these types but each is <80% of the tumour area.
— tubulolobular: classical pattern with focal microtubules which are less distinct than in tubular carcinoma.

Special types
— tubular: round, ovoid, angular tubules/single cell layer/cytoplasmic apical snouts/fibrous stroma.
— cribriform: invasive cords and islands with the morphology of cribriform DCIS comprising punched out lumina and cytoplasmic apical snouts.
— colloid (mucinous): pushing margins, extracellular mucin with small clusters (10–100 cells) of uniform epithelial cells.
— papillary: encysted (intracystic) in-situ or invasive. Invasion is either (a) a dominantly invasive carcinoma with a pushing margin and papillary pattern, or (b) an encysted papillary carcinoma with focal invasion and the invasive component can be papillary or ductal, NST. Note also invasive micropapillary carcinoma (micropapillae without cores set in clear spaces—the "inside-out" tumour with an external rim of apical cytoplasm), which correlates with lymphovascular and axillary node metastases. Also seen as a component of 5% of ductal, NST tumours.
— medullary, classical: sharply circumscribed margin, >75% is patternless tumour cell syncytium with grade 3 cytology, peri-/intratumoral stromal lymphoplasmacytic infiltrate with absence of glands and scant fibrous stroma.
— medullary, atypical: contains up to 25% ductal, NST, or an irregular margin with focal infiltration, or adjacent DCIS. Probably better regarded as invasive ductal, NST, with medullary features. The term medullary-like carcinoma has been suggested to encompass both classical and atypical medullary cancers, particularly as the observer reproducibility rates are so low.

Mixed types
— 10% of breast cancers.
— mixed differentiation ductal and lobular.
— tubular mixed—stellate mass, central tubules with peripheral less differentiated adenocarcinoma.

Others
— metaplastic: biphasic epithelial (ductal in situ/invasive NST grade 2/3, or squamous) and sarcomatous elements (carcinosarcoma) or pure monophasic spindle cell carcinoma (cytokeratin/EMA/p63 positive).

The sarcomatous element is either fibrosarcomatous/malignant fibrous histiocytoma-like or chondro-, osteo-, leiomyo-, rhabdomyo- or liposarcomatous. Represents carcinoma with a spectrum of malignant spindle cell stroma which can be homologous or heterologous. Behaves as a high-grade carcinoma or sarcoma with haematogenous metastases. The epithelial component may be minor and require multiple blocks to demonstrate.

— pleomorphic carcinoma: high-grade ductal cancer with background spindle cells and >50% bizarre giant cells (cytokeratin positive). Presents with advanced disease.
— carcinoma with osteoclast giant cells (CD68 positive).
— signet ring cell carcinoma: lobular carcinoma or gastric carcinoma analogues.
— small cell: rare, aggressive, ± chromogranin/synaptophysin/CD56 positive.
— other neuroendocrine: invasive ductal carcinoma with endocrine differentiation; variable nests, spindle cells or large cells, or carcinoid-like.
— secretory: one-third are in children, indolent, good prognosis. Two-thirds are in adults and more aggressive. Tubular/solid/honeycomb patterns; PAS/AB-diastase positive luminal secretions.
— squamous cell: primary or secondary from breast skin or metastatic, e.g. lung. Also distinguish from metaplastic breast carcinoma.
— clear cell: glycogen rich and worse prognosis.
— mucoepidermoid: grade determines prognosis with cystic/mucin secreting better than solid/epidermoid variants.
— adenoid cystic: indolent with late recurrence. Salivary gland tumour analogue.
— apocrine: rare, cytoplasmic apical snouts, GCDFP-15 positive.
— adenomyoepithelioma: elderly, of low malignant potential and characterized by sheaths of proliferating clear myoepithelial cells around epithelial lined spaces. Occasionally malignant myoepithelioma (spindle cells with mitoses).

Pure carcinoma

— ≥90% of the tumour volume.

Mixed carcinoma

— 50–90% of the tumour comprises a special type component.

Metastatic carcinoma

— often solitary, upper outer quadrant at a late stage in known carcinomatosis. The majority of childhood breast malignancy is metastatic, e.g. alveolar rhabdomyosarcoma. In adults, usually lung (small cell), malignant melanoma, lymphoma/leukaemia, but also ovary, contralateral breast (usually this represents a metachronous primary), gut, kidney, thyroid carcinomas and small intestinal carcinoid tumour. A relevant clinical history, absence of in-situ change and mul-

tiple intravascular deposits are pointers to metastases. Specific combinations of antibodies e.g. CK7/TTF-1 (lung), paranuclear dot CAM5.2/chromogranin/synaptophysin/CD56 (small cell), S100/HMB-45/melan A (melanoma), CD45/CD20/CD3/CD68/myeloperoxidase (lymphoma/leukaemia), CA125/CK7/WT-1 (ovary), CK20/CDX-2 (gut), RCC ab/EMA/vimentin (kidney), thyroglobulin/TTF-1 (thyroid) and immune markers of breast profile (e.g. ER/PR, cytokeratin 7, CEA, GCDFP-15) may be helpful in distinguishing between primary breast and non-mammary disease. Metastatic tumour should be considered in any breast lesion with unusual clinical, radiological, gross or histological features.

3. DIFFERENTIATION/GRADE

Well/moderate/poor, or Grade 1/2/3.
See protocol: Grading of Invasive Breast Carcinoma.

4. EXTENT OF LOCAL TUMOUR SPREAD

Border: pushing/infiltrative.
Lymphocytic reaction: prominent/sparse.
Quadrant(s):

— Paget's disease.
— skin involvement (direct extension or lymphatics).

pT is based on the maximum dimension of invasive cancer and not whole size measurements that include adjacent DCIS.

The TNM classification applies to carcinoma of the female and male breast

pTis carcinoma in situ: DCIS, LCIS or Paget's with no tumour
pT1 tumour ≤ 2 cm

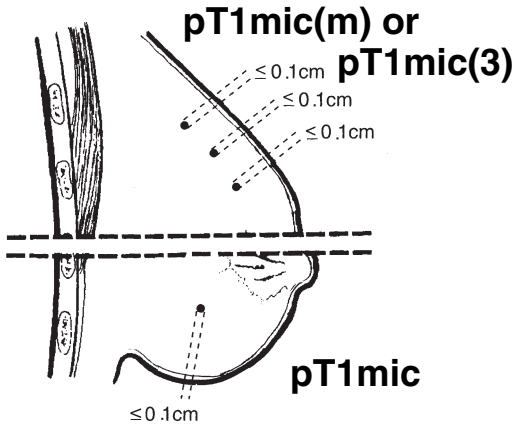


FIGURE 22.4. Breast carcinoma.

	T1 mic	≤0.1 cm
	T1 a	0.1 cm < tumour ≤ 0.5 cm
	T1 b	0.5 cm < tumour ≤ 1 cm
	T1 c	1 cm < tumour ≤ 2 cm
pT2	2 cm < tumour ≤ 5 cm	
pT3	tumour > 5 cm	

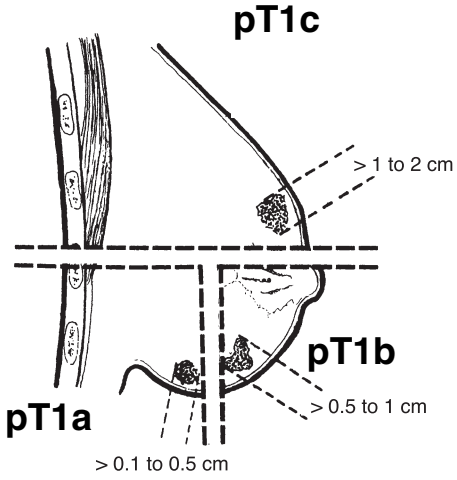


FIGURE 22.5. Breast carcinoma.

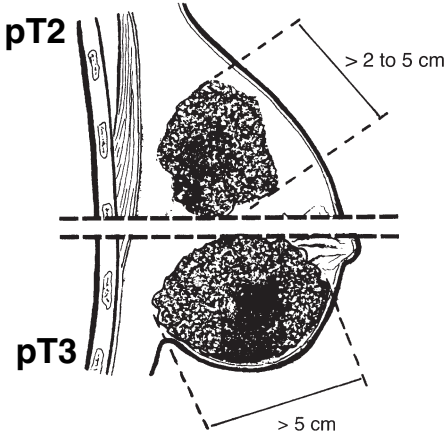


FIGURE 22.6. Breast carcinoma.

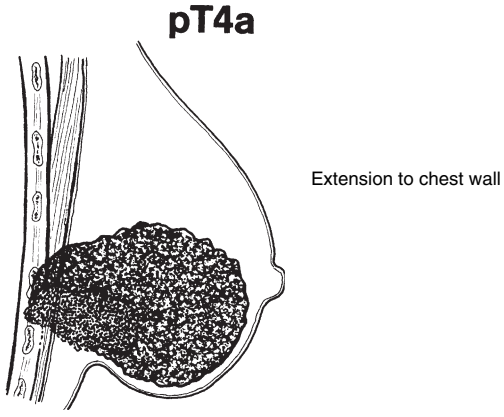


FIGURE 22.7. Breast carcinoma.

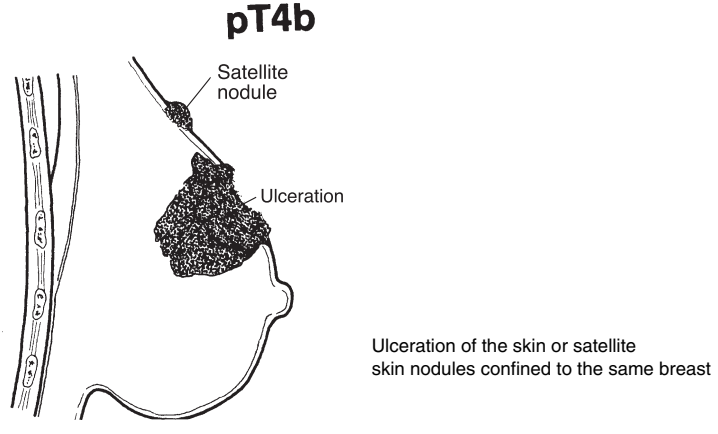


FIGURE 22.8. Breast carcinoma.

pT4 tumour any size with direct extension to chest wall (ribs, intercostal muscles, serratus anterior but not pectoral muscle) or skin*
(a) chest wall
(b) oedema including peau d'orange, skin ulceration or satellite nodules† in the same breast

*Dermal invasion alone without ulceration, satellite nodules or inflammatory carcinoma does not constitute pT4.
†Clinical or grossly apparent skin satellite nodules, not just histological foci.

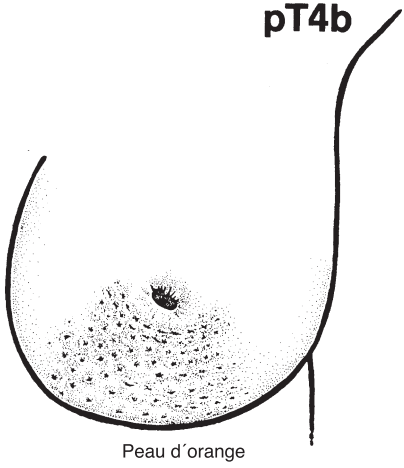
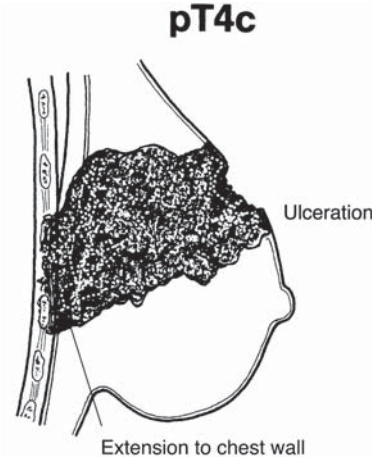


FIGURE 22.9. Breast carcinoma.



pT4c = pT4a + pT4b

FIGURE 22.10. Breast carcinoma.

(c) a and b
(d) inflammatory carcinoma.

Clinically sore and red due to tumour involvement of dermal lymphatics and often without an underlying palpable mass. It can be difficult to obtain tissue proof on FNA cytology or needle core biopsy. The malignant cells are usually ductal, NST, grade 3.

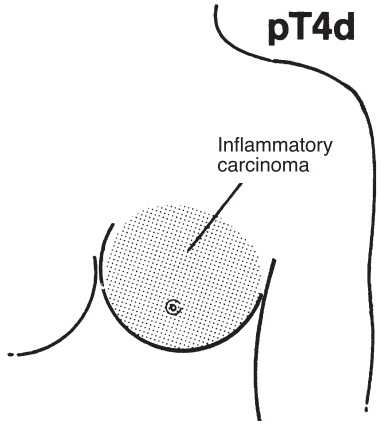


FIGURE 22.11. Breast carcinoma.

In-situ change

— present/absent.
— intra-/extratumoral: >1 mm outside the main tumour mass and its extent.

Pure DCIS of limited size (<4 cm) tends to be unicentric (albeit ramifying through the involved duct system) and treated by breast-conserving surgery with adjuvant radiotherapy. If it is mammographically extensive mastectomy is done. If it forms more than 25% of an invasive cancer and is present away from it in a local excision specimen, it constitutes an extensive intraductal component (EIC) which is an indication for considering proceeding to mastectomy and/or radiotherapy. DCIS is also assessed for oestrogen receptor status as a guide to potential hormonal treatment response.

— architectural pattern: solid/cribriform/(micro-)papillary/comedo.
— cytonuclear grade: shows less heterogeneity and higher interobserver agreement than architectural pattern. It is now the favoured method for grading ductal carcinoma in situ using either nuclear features alone (NHS Breast Screening Programme) or combined with the presence of comedonecrosis (Van Nuys classification). High grade correlates with a greater frequency of concurrent or subsequent invasive carcinoma.

Not infrequently there is correlation between DCIS architectural pattern and cytonuclear grade, e.g. comedonecrosis is high grade and cribriform low grade. However, this is not always the case, e.g. solid or micropapillary, although usually low to intermediate grade, can be high grade.

5. LYMPHOVASCULAR INVASION

Present/absent.
Intra-/extratumoral: >1 mm outside the main tumour mass.

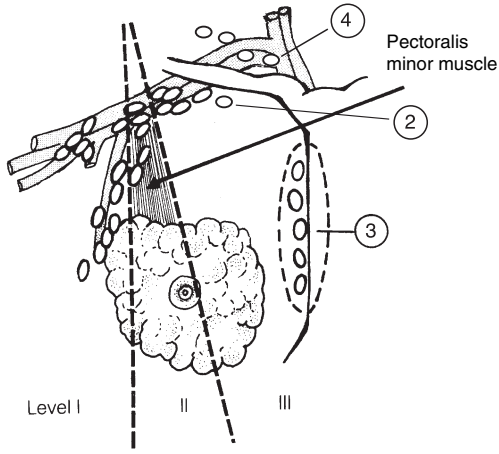


FIGURE 22.12. Breast carcinoma: axillary lymph nodes.

The commonest site for vascular invasion is at the tumour edge and it is present in about 25–35% of cases.

6. LYMPH NODES

Site/number/size/number involved/apical node/extracapsular spread.
Regional nodes: axillary (levels I, II, III and intramammary), ipsilateral infraclavicular (②), internal mammary (③) and supraclavicular (④). Any other nodal metastasis is regarded as a distant metastasis pM1, including cervical or contralateral internal mammary. A regional lymphadenectomy will ordinarily include a minimum of six lymph nodes (level I) and in practice more often between 15 and 30 (levels I, II and III).

Axillary lymph nodes

They receive ≥75% of the lymphatic flow.

Level 1: low axilla. Nodes lateral to the border of pectoralis minor muscle
Level 2: mid-axilla. Nodes between the medial and lateral borders of the pectoralis minor muscle
Level 3: apical axilla. Nodes medial to the medial margin of the pectoralis minor muscle.

pN0 no regional lymph nodes metastasis
pN1 a. metastasis in 1–3 ipsilateral node(s)
b. internal mammary node(s) with microscopic metastasis by sentinel node biopsy but not clinically apparent*
c. = a + b

*Clinically apparent = detected by clinical examination or by imaging studies (excluding lymphoscintigraphy) or grossly visible pathologically.

pN2 a. metastasis in 4–9 ipsilateral axillary nodes
b. in clinically apparent internal mammary node(s) but without axillary nodes
pN3 a. metastasis in ≥10 axillary nodes or infraclavicular node(s)
b. metastasis in clinically apparent internal mammary node(s) with axillary nodes, or metastasis in >3 axillary nodes and in internal mammary nodes with microscopic metastasis by sentinel node biopsy but not clinically apparent.
c. metastasis in supraclavicular node(s).

Sentinel node staging is designated pN0 or pN1(sn).

Cytokeratin markers are useful where the morphological appearances are suspicious, but not diagnostic of metastatic carcinoma, e.g. sinusoidal lobular carcinoma cells vs. sinus histiocytosis. The significance of nodal micrometastases (≤2 mm: pN1mi) remains uncertain, with some regarding it as an adverse prognostic indicator but others less convinced. From a practical viewpoint it does influence choice of systemic adjuvant chemotherapy and hormonal therapy and should be reported. The biological status of isolated tumour cells (≤0.2 mm: pN0) is not established. Histological levels of serial slices and cytokeratin immunostaining may be necessary, particularly if sentinel node biopsy (95% positive predictive value for axillary node metastasis) alone is used for staging purposes in clinically node-negative patients. Other recommended approaches to axillary disease are axillary node sampling (3 or 4 level I nodes for staging only) or axillary node clearance (for staging and treatment). Axillary node involvement is seen in 40–50% of cases. Of these patients with axillary nodal disease there can also be involvement of the internal mammary chain (22%) and supraclavicular nodes (20%). Distant metastases are to the skeleton, lung and pleura, liver, ovary, adrenal gland and CNS. Presentation with metastatic tumour in axillary nodes is usually due to either breast carcinoma or malignant melanoma and this can be resolved with immunostaining. The source of the breast carcinoma is usually the ipsilateral breast or axillary tail of breast and the lesion can be clinically difficult to locate as its size is often less than 2 cm in diameter. Interestingly, invasive lobular carcinoma has a greater tendency than ductal tumours to metastasize to retro-/peritoneum, meninges, gastrointestinal and female genital tracts.

7. EXCISION MARGINS

Measure the distances (mm) to the nearest and other painted margins (superficial, deep, lateral, medial, inferior, superior). Differential block labelling and use of multi-coloured inks are important. Separate orientated cavity margin samples may also be submitted by the surgeon.
Adequate clearance of margins is:

— invasive carcinoma 5 mm.
— in-situ carcinoma 10 mm (ductal only as lobular can be multifocal).

Involved margins may be an indication for either radiotherapy (deep, superficial margins) or further surgery as a local re-excision (site oriented

cavity shavings) or conversion to a mastectomy (other margins). Note that they can be particularly difficult to define and assess in lobular carcinoma when distinction from fibrous breast tissue can be problematic. Margin involvement in DCIS is a strong predictor of local recurrence, about 50% of which will be as invasive disease, particularly so for high cytonuclear grade DCIS and often correlating with high-grade cancer.

8. OTHER PATHOLOGY

Assess breast tissue away from the tumour for:

Atypical hyperplasia, carcinoma in situ, satellite invasive foci, LVI.

Carcinoma in situ and LVI away from (>1 mm) the tumour are strong prognostic indicators of local and nodal recurrence and are important in selecting appropriate postoperative adjuvant therapy or further surgical excision. Relationship of satellite invasive foci to margins must also be assessed and they occur more frequently in infiltrating lobular carcinoma.

Atypical hyperplasia (ductal and lobular) is regarded as having × 4–5 increased risk of subsequent carcinoma and in-situ change × 10–11 increased risk over control populations. The precancerous nature of atypical hyperplasia is illustrated by its shared molecular abnormalities (e.g. loss of allelic heterozygosity) with carcinoma in situ. There is also now some evidence for a flat (columnar) cell hyperplasia with atypia—ADH–DCIS–cancer sequence. LCIS is usually an incidental microscopic finding, e.g. adjacent to a simple cyst or present (60%) in the vicinity of invasive lobular cancer and it is potentially multifocal and bilateral. Ductal carcinoma in situ may present as Paget's disease ± nipple discharge, a tumour-forming mass (especially comedo type with a greater propensity for invasive carcinoma), adjacent to a symptomatic invasive breast cancer, an incidental finding on open biopsy or as an impalpable lesion detected on radiological screening (15–20% of screening cancers). This can be either as linear, branching calcifications or within the context of a radiologically suspicious but histologically benign lesion, e.g. radial scar/complex sclerosing lesion. Immunomarkers S100, h-caldesmon, calponin, smooth muscle actin and cytokeratin 5/6 are useful in demonstrating a myoepithelial cell layer as an aid to distinction from invasive carcinoma.

It is essential to correlate the clinical mammographic abnormality with the excised specimen. This requires dissection guided by the postoperative specimen radiograph demonstrating the lesion in question with or without an in-situ localization needle. The histological slides must contain the abnormality, e.g. carcinoma or microcalcification and, if not, all of the residual tissue processed or further blocks selected according to radiographic study of the specimen serial slices. Usual calcification (calcium phosphate) is easily recognizable as basophilic in routine sections. A minority (10%) is oxalate in character, can be partially removed by tissue processing and is recognized by being doubly refractile on polarization. It is usually seen in benign disease, e.g. fibrocystic disease. Similarly, needle core biopsy for microcalcification requires X-ray of the core to ensure that the relevant area has been sampled.

Paget's disease (2% of breast cancer patients) is distinguished immunohistochemically from malignant melanoma and Bowen's disease by being mucin, CEA, EMA, Her-2 (50%) and cytokeratin 7 positive, and AE1/AE3, S100, HMB-45 and melan-A negative. DCIS of large cell type is nearly always identified in the subareolar duct system and there is associated invasive breast carcinoma in 35–50% of cases. Depending on the mammographic extent of the underlying lesion (size, in situ vs. invasive), partial or total mastectomy is carried out.

Microinvasion, defined as <1 mm from the nearest basement membrane (infiltration of non-specialized interlobular/interductal stroma), must be distinguished from the more frequent cancerization of lobules (lobular architecture/intact basement membrane) and clinically is managed as DCIS as the incidence of axillary lymph node metastases is very low. The likelihood of invasion increases with the grade of DCIS, e.g. comedocarcinoma and extra blocks and levels should be assessed. Usually the type of invasive carcinoma correlates with the type of DCIS, but LCIS can be associated with invasive carcinoma of ductal or lobular type.

Neoadjuvant chemo-/radiotherapy effects include tumour cell necrosis, degeneration, apoptosis, vacuolation, inflammation and fibrosis, and tends to be reserved for pT3/pT4 tumours, which may then be followed by surgical resection. It improves resectability and may have a role to play in downstaging of the tumour, although this is not yet clarified. It also makes tumour typing and grading difficult, features that are perhaps better assessed on the pretreatment needle core biopsy. Tumour size may also need to be based on the radiographic or ultrasound measurements. Postoperative radiotherapy is used for the control of local recurrence in the presence of positive deep or superficial margins of excision and can result in diagnostically confusing cytological atypia in native ductulolobular unit epithelium. The presence of widespread metastatic disease should be clinically determined prior to surgical resection so that palliative systemic therapy can be considered. Localized disease is treated by wide local excision ensuring 10–20 mm palpable margins of clearance around the tumour. Conversion to mastectomy (10–15% of cases) is undertaken in the following combination of circumstances: if the patient is <50 years of age, has a tumour diameter >2 cm, has lymphovascular invasion or involvement of the surgical margins. Otherwise the intact breast receives radiotherapy. Mastectomy is indicated as initial treatment if the tumour is centrally situated (behind the nipple), >3 cm in diameter and/or associated with radiological evidence of extensive DCIS, or if it is the patient's preference.

Triple assessment and concordance of its three modalities (clinical examination, radiology, FNA cytology (FNAC) ± needle core biopsy) have replaced frozen section and the majority of open biopsies in the diagnosis of breast carcinoma. This allows a one-stop assessment and progression to definitive breast-conserving or more radical surgery. Open biopsy may still be required where there is discordance between the parameters. FNAC cannot accurately distinguish between in-situ and invasive malignant cells and supplementary core biopsy is advantageous, e.g. high-grade ductal carcinoma in situ. Note that diagnostic core biopsy can

underestimate cancer grade and may not accurately reflect tumour subtype compared with the resection specimen, e.g. for reasons of tumour heterogeneity in both cellularity and differentiation. Core biopsy is also advantageous when FNAC is either insufficient (e.g. scirrhous or lobular carcinoma) or inconclusive (e.g. some well-differentiated grade I cancers), and also in the neoadjuvant setting for determination of tumour oestrogen/progesterone/Her-2 receptor status. Potential diagnostic pitfalls in core biopsies are overcall of: sclerosing adenosis/radial scar/complex sclerosing lesion as tubular carcinoma, apocrine atypia as DCIS, chronic inflammation (cytokeratin negative) as lobular carcinoma and radiotherapy changes as carcinoma. False-negative diagnosis includes the reverse of the above, metaplastic carcinoma mistaken for a fibrous scar, undercalling of DCIS as ADH, and invasive cancer due to sampling limitations. Carcinoma is the outcome in up to 20% of subsequent resection specimens for ADH/DCIS seen on needle biopsy.

Prognosis

Prognosis relates to patient age, tumour size, grade, lymphovascular invasion, nodal and hormonal status. Nodal/Her-2 positive disease equates to high risk. Nottingham Prognostic Index (NPI) = 0.2 × invasive tumour size (cm) + stage + tumour grade.

			Score
Stage	A	No nodes involved	1
	B	≤3 low axillary nodes involved	2
	C	≥4 nodes and/or the apical node involved	3

NPI score	Prognosis	5-year survival
<3.4	Good	88%
3.4–5.4	Intermediate	68%
>5.4	Poor	21%

Dutch workers advocate a morphometric index based on tumour size, mitotic activity index and lymph node status as giving practical clinical prognostic data. Age < 35 years is also adverse.

Overall 5-year survival is 60% for clinically localized disease and 34% for regional disease.

Prognosis according to histological type (10-year survivals):

excellent (>80%)	tubular, cribriform, mucinous, tubulolobular, encysted in-situ papillary
good (60–80%)	tubular mixed, alveolar lobular, mixed ductal NST/special type
intermediate (50–60%)	classical lobular, medullary, invasive papillary
poor (<50%)	ductal (no special type), mixed ductal and lobular, solid and pleomorphic lobular, metaplastic.

Oestrogen/progesterone receptor expression

Positive in 70–80% of ductal (usually grade 1/2) cancers and 70–90% of infiltrating lobular carcinomas.

Most postmenopausal patients receive the anti-oestrogen tamoxifen but positive oestrogen receptor (ER) status in premenopausal patients is important so that consideration can be given to hormonal treatment. Progesterone receptor expression is a prognostic marker and may also indicate hormone responsiveness.

— tissue for staining: choose block (formalin fixed) with tumour and normal breast elements (internal control).
— staining method: Ventana Medical Systems DAB Detection Kit with 2 min pressure cooking heat-mediated antigen retrieval (HMAR).
— monoclonal antibody: Ventana 760-2596 clone 6F11; PR—DAKO M3569 clone PgR 636; Her-2—DAKO A0485 (HMAR 1′ 30″).

Scoring system: "Category Score"

Staining characteristics	Microscopic assessment	ER status
Negative	No staining	ER–
Weak	×25, ×40 objective	ER+
Moderate	×10 objective	ER+
Strong	×10 objective	ER+

Scoring system: "Histo Score"

In the Histo score, each cell is assessed as:

0—no staining
1—weak staining
2—moderate staining
3—strong staining.

The percentage of cells showing each intensity of staining is estimated over as much of the section as possible and the Histo Score is calculated by multiplying the intensity score by the percentage of tumour cells showing that intensity: e.g. a tumour with 50% of cells strongly stained, 25% moderately stained and 25% weakly stained would score $(50 \times 3) + (25 \times 2) + (25 \times 1) = 225$. Histo Scores <75 are considered to be ER negative and those >75 are considered to be ER positive.

Scoring system: "Quick score"

In the Quick score, the proportion of cells staining and their intensity are assessed as:

Proportion	0 = no nuclear staining
	1 = <1% nuclei staining
	2 = 1–10% nuclei staining
	3 = 11–33% nuclei staining
	4 = 34–66% nuclei staining
	5 = 67–100 % nuclei staining
Intensity	0 = no staining
	1 = weak staining
	2 = moderate staining
	3 = strong staining.

Adding the two scores together gives a maximum score of 8 with the likelihood of anti-oestrogen responsiveness being

0 hormonal therapy will not work
2–3 a small (20%) chance of treatment response
4–6 an even (50%) chance of treatment response
7–8 a good (75%) chance of treatment response

Currently the Quick score is the recommended method of assessment.

Individual cancers can show heterogeneity of ER receptor expression and in some respects the Histo and Quick Scores can take this into account. Carcinoma in situ (low to intermediate-grade), infiltrating lobular carcinoma, low-grade invasive ductal carcinoma and postmenopausal cancers tend to be ER positive, while high-grade in-situ and invasive ductal lesions and a significant number of premenopausal carcinomas (grade-related) are ER negative. In practice with improved immunocytochemistry the vast majority of breast cancers are either strongly positive or completely negative for ER and assessable at a glance. Quantifying PR expression can be less clear-cut.

Her-2 neu (c-erbB2) expression

Her-2 overexpression (15–30% of breast cancers) is associated with high-grade in-situ and grade 2/3 invasive ductal and pleomorphic infiltrating lobular cancers, and ER negative, recurrent or metastatic tumours. It can indicate potential resistance to Tamoxifen and CMF (Cyclophosphamide, Methotrexate, Fluorouracil) chemotherapy but benefit from high-dose adriamycin or Herceptin/Trastuzumab monoclonal antibody therapy. It is assessed as negative (0–1+), equivocal (2+) or positive (3+). Equivocal cases (2+) are then subjected to fluorescent in-situ hybridization (FISH) analysis for Her-2 gene amplification (25–30% positive).

0 membrane staining in <10% of cells
1+ weak incomplete membrane staining in >10% of cells
2+ weak or moderate complete membrane staining in >10% of cells
3+ strong complete membrane staining in >10% of cells.

The role of serum Her-2 testing is currently being investigated.

Immunophenotype: miscellaneous markers for breast cancer

— Ki-67 proliferation index (percentage positive cells), Her-2, p53, DNA ploidy.
— decreased survival is associated with tumours that are ER/PR negative, DNA aneuploid, overexpress p53/Her-2 and have a high proliferation index.
— cytokeratin (CAM5.2, AE1/AE3, CK7), GCDFP-15, EMA, CEA positive. Variably positive for HMB-45, S100 and vimentin.
— cytokeratin 7 positive/20 negative: the reverse of this is seen in intestinal tract tumours and this can be useful in metastatic carcinoma of uncertain origin, e.g. signet ring cell carcinoma.
— myoepithelial markers to distinguish radial scar/complex sclerosing lesion from tubular carcinoma and in-situ from invasive ductal cancer: S100, h-caldesmon, calponin, p63, smooth muscle actin, cytokeratin 5/6.

— E-cadherin: loss of expression in ALH/LCIS and infiltrating lobular carcinoma but retention in ductal lesions. Conversely, 34βE12 is expressed in LCIS but lost in DCIS.
— usual ductal hyperplasia is 34βE12, CK5/6 and CK14 positive, whereas ADH/DCIS is negative for these markers but positive for CK8 and CK18, indicating an absence of the mixed luminal/basal epithelial differentiation that is present in usual hyperplasia.

9. OTHER MALIGNANCY

Leukaemia
— single/multiple, uni-/bilateral.
— during the course of known disease or as a primary clinical presentation.
— ALL/CLL/myeloma (κ, λ light chain restriction and clinical evidence of systemic disease).
— granulocytic sarcoma (CD68/chloroacetate esterase/myeloperoxidase positive) can mimic infiltrating lobular carcinoma (cytokeratins, cellular mucin) and lymphoma (CD45, CD20, CD3).

Lymphoma
— usually secondary to known nodal/systemic disease and not biopsied.
— 0.5% of primary malignant breast tumours.
— may present clinically and radiologically as a carcinoma and immunostaining of aspirate and/or biopsy material will be necessary.

Primary lymphoma (by exclusion of systemic lymphoma after staging):

1. commonest:	aggressive large B-cell lymphoma usually unilateral in elderly women
2. secondly:	aggressive Burkitt's/Burkitt's-like lymphoma in young pregnant or lactating women. Bilateral with CNS and ovarian involvement.
3. rarely:	indolent low-grade MALToma (?prior lymphocytic lobulitis).
4. differential diagnosis:	infiltrating lobular carcinoma, medullary carcinoma; immuno-cytokeratins, CD45, CD20, CD3. ER can be positive in carcinoma and lymphoma.
5. prognosis:	overall 48% 5-year survival; Burkitt's, poor.

Phyllodes tumour
— benign/borderline/malignant comprising a biphasic proliferation of double-layered hyperplastic epithelium and abundant, cellular mesenchymal elements with a leaf-like architecture.

Designation is based on:

1. circumscribed or infiltrative margins
2. stromal cellularity
   overgrowth (absence of epithelium in one low power field)

atypia
mitoses >5–10/10 hpfs = probably malignant when combined with overgrowth and atypia
mitoses >10/10 hpfs = malignant
overexpression of p53.

A majority is benign, but local recurrence is not uncommon and a small number develop haematogenous metastases to lung and bone. Axillary lymph node metastases are rare. At the benign end of the spectrum the differential diagnosis is cellular fibroadenoma and at the malignant end metaplastic breast carcinoma (cytokeratin positive) and sarcoma. Mammography and FNAC are not particularly accurate at diagnosing phyllodes tumour. Wide (1-cm margins) local excision is needed for histological designation and prevention of local recurrence, which can occur even with benign and borderline lesions. Those classified as malignant have metastatic potential.

Sarcoma

Sarcoma (<1% of breast malignancies), e.g. angiosarcoma (± post radiotherapy) and other primary soft tissue sarcomas (in decreasing order of frequency): malignant fibrous histiocytoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma, leiomyosarcoma. Prognosis relates to high histological grade, mitotic counts and infiltrating margins. Important and more common differential diagnoses are metaplastic breast carcinoma (identify epithelial component, cytokeratin positive) and malignant phyllodes tumour (biphasic and typical architecture). Angiosarcoma is the commonest primary breast sarcoma, occurs in middle-aged to elderly women and is on average 5 cm in diameter with poorly defined margins. Grade 1 lesions (40%) must be distinguished from haemangioma and pseudoangiomatous hyperplasia and have an 81% 10-year survival. Grade 3 lesions (40%) mimic poorly differentiated carcinoma and have 10% 10-year survival with metastases to lungs, liver, skin, bone and brain. Diagnosis can be difficult on FNAC and biopsy is required. Angiosarcoma is variably factor VIII, CD34 and CD31 positive.

Other spindle cell lesions of the breast to be considered in a differential diagnosis are: metastatic malignant melanoma and sarcomatoid renal cell carcinoma, fibromatosis and myofibroblast-related lesions (inflammatory myofibroblastic tumour, myofibroblastoma).

REPORTING CATEGORIES FOR BREAST FINE NEEDLE ASPIRATES AND WIDE BORE NEEDLE CORE BIOPSIES

FNAC is highly efficient and accurate at diagnosing a wide range of breast disease when interpreted in conjunction with the patient's age, clinical history, clinical features of the lesion and its radiological appearances. Two basic patterns are encountered:

1. Benign
   - a biphasic pattern of cohesive breast epithelium and background bare nuclei
   - low to moderate cellularity (except fibroadenoma, which is of high cellularity)

2. Malignant — dyscohesive clusters and singles of variably atypical epithelial cells
cytoplasmic preservation in dispersed cells
absence of bare nuclei
stripped (bare) malignant nuclei
moderate to high cellularity for the patient's age.

FNAC reporting categories are:

C1 an inadequate specimen: insufficient epithelial cells, epithelial cell content obscured by inflammation or a technically poorly prepared smear
C2 an adequate benign specimen: of sufficient cellularity and showing a benign biphasic pattern
C3 atypia, benign: showing some mild nuclear change or cellular dissociation but within an essentially benign pattern
C4 atypia, suspicious: a pattern and cell constitution suspicious but not diagnostic of malignancy for quantitative (inadequate cellularity) or qualitative (insufficient atypia) reasons
C5 malignant: a cellular specimen showing an unequivocally malignant pattern and individual malignant cells.

FNAC is supplemented by wide bore needle core biopsy in certain circumstances, e.g. the diagnosis of phyllodes tumour, infiltrating lobular carcinoma (which may be scanty on FNAC) and the distinction between in-situ and invasive malignancy (the latter being an indication for axillary lymph node staging/resection).

Wide bore needle core biopsy reporting categories are:

B1 unsatisfactory/normal tissue only
B2 benign: e.g. fibroadenoma, sclerosing adenosis
B3 benign but of uncertain malignant potential: benign lesions associated with the presence of cancer and/or the risk of developing it, e.g. radial scar/complex sclerosing lesion, atypical ductal hyperplasia, ALH/LCIS, phyllodes tumour, papillary lesions
B4 suspicious of malignancy: epithelial proliferation suspicious but not diagnostic of malignancy for quantitative or qualitative reasons
B5 malignant: a. in situ
b. invasive.

Reporting categories are a useful tool in the day-to-day management of individual cases and crucial for clinicopathological audit purposes. It is imperative that FNAC and wide bore needle core biopsy material are closely correlated with their respective surgical specimens.

GRADING OF INVASIVE BREAST CARCINOMA

Grading is most relevant to infiltrating duct carcinoma, no specific type, and although more difficult to apply to special cancer types can give additional prognostic information. Infiltrating lobular carcinoma tends to be given grade 2, although the classical and pleomorphic variants score

as grades 1 and 3, respectively. The Elston-Ellis modification of the Scarff-Bloom-Richardson system is used. There can be tumour grade heterogeneity and tubule formation takes this into account as it is based on the whole tumour area. However, nuclear features and mitoses are assessed on the least differentiated area.

Three parameters are assessed and scored:

	Score
1. Tubule formation	
Majority of tumour (>75%)	1
Moderate (10–75%)	2
Little or none (<10%)	3
2. Nuclear pleomorphism	
Small regular, uniform	1
Larger with variation	2
Marked variation in size and shape (± multiple nucleoli)	3

3. Mitoses (tumour periphery and most active areas rather than the paucicellular centre). The mitotic count (number of mitoses per 10 hpfs) is related to the objective field diameter:

Leitz Diaplan ×40 obj.	Leitz Ortholux ×25 obj.	Nikon Labophot ×40 obj.	
0–11	0–9	0–5	1
12–22	10–19	6–10	2
>22	>19	>10	3

Total score	Grade	
3–5	1	Well differentiated
6–7	2	Moderately differentiated
8-9	3	Poorly differentiated.

Gynaecological Cancer

- Ovarian Carcinoma (with comments on fallopian tube carcinoma)
- Endometrial Carcinoma
- Cervical Carcinoma
- Vaginal Carcinoma
- Vulval Carcinoma
- Gestational Trophoblastic Tumours

23

Ovarian Carcinoma (with comments on fallopian tube carcinoma)

1. GROSS DESCRIPTION

Specimen

— fine needle aspirate/wedge biopsy/oophorectomy and/or cystectomy/uni-/bilateral salpingo-oophorectomy ± hysterectomy/omentectomy/lymphadenectomy.
— weight (g) and size (cm).
— peritoneal washings. If diagnostic ascitic fluid has not been previously submitted or is not present at laparotomy, peritoneal staging washings are carried out. The pathologist should correlate the histological and cytological findings to determine an appropriate tumour stage. Distinction between hyperplastic mesothelial cells and borderline/malignant serous epithelial cells can be particularly problematic, emphasizing the need for close correlation.
— presentation of ovarian cancer in 70% of cases is late at an advanced stage of disease and with non-specific symptoms such as abdominal fullness or swelling. A high risk-malignancy index equates to post menopausal status, a solid or cystic lesion with septation on abdominal ultrasound scan and elevated serum CA125. Further investigations include CT scan chest/abdomen/pelvis and peritoneal ascitic fluid aspiration for cytology. If a benign cyst is suspected FNA may be used or unilateral salpingo-oophorectomy considered, particularly in a young woman of childbearing age. Otherwise suspected malignant ovarian lesions are treated by total abdominal hysterectomy and bilateral salpingo-oophorectomy with omentectomy.

Tumour

Site

— ovarian (cystic, cortical, medullary, hilar or serosal)/paratubal/broad ligament.
— serosal tumour is associated with a worse prognosis than an equivalent cortical or intracystic lesion. Medullary, hilar or paraovarian tumour nodules may indicate a metastatic deposit rather than a primary lesion.
— unilateral/bilateral (30–40% of serous epithelial lesions).

Size
— length × width × depth (cm) or maximum dimension (cm).

Appearance
Capsule: intact/deficient, smooth/rough.
Cut surface:

— cystic: uni-/multilocular
warty growths/nodules
fluid contents: serous/mucoid
sebaceous content: hair/teeth/colloid (struma ovarii)
— solid: partially/totally (cm)
necrosis/haemorrhage.
— ovarian cancer tends to have a mixed cystic and solid appearance. The former comprises uni-/multiloculated thin-walled cysts with warty/nodular/papillary/solid areas of tumour growth which can be internal (endophytic) or serosal (exophytic). In lesions with a smooth external surface, areas of capsular deficiency should be actively sought and the relationship to any tumour noted, either caused by it (due to capsular infiltration), or overlying or away from it. The latter may be due to surgical dissection through a plane of adhesions or intra-operative rupture because of the size/cystic nature of the lesion, respectively. It is therefore important to determine the mechanism and part of the tumour that is deficient or ruptured in assessing potential spillage of benign, borderline or malignant cells into the peritoneal cavity so that the clinicopathological meeting can assign an appropriate FIGO/TNM stage. The solid component of ovarian cancer tends to be somewhat friable and pale in appearance. Other visual diagnostic clues include: granulosa cell tumour (pale/fleshy/cystic), steroid cell tumour and carcinoid (yellow), thecoma/fibroma (white, whorled cut surface with yellow areas, lobulated), metastatic melanoma (pigmented), immature teratoma (dermoid cyst with solid areas other than calcification/teeth), malignant lymphoma (pale/fleshy) and metastases (multiple, nodular corticomedullary/ serosal/ para-ovarian/paratubal deposits).

Edge
— circumscribed/irregular.

Fallopian tube: length (cm); infiltration of paratubal connective tissue.

Omentum: weight (g) and size (cm); tumour nodules: number/maximum dimension (cm).

2. HISTOLOGICAL TYPE

Epithelial and sex cord stromal lesions form 60–70% of ovarian tumours (75% of which are benign) and 90–95% of primary ovarian malignancy, the majority of which arises from the surface (coelomic) epithelium. Epithelial tumours are classified according to their cell type, growth pattern (solid, cystic, surface), amount of fibrous stroma and neoplastic potential of the constituent epithelium (benign, borderline or malig-

nant/invasive). Germ cell tumours comprise 25% of ovarian tumours and the vast majority of these are benign. They form 60–70% of childhood ovarian tumours and while the majority of these are benign (cystic teratoma), there is a greater proportion of malignant germ cell tumours (immature teratoma, yolk sac tumour) than in adults.

Epithelial

— serous 45%
— mucinous 15%
— endometrioid 20%
— clear cell 10%
— Brenner 2%

} benign, borderline or malignant

— mixed: either of different epithelial subtypes or differentiation within one subtype
  - mucinous cystadenoma/Brenner tumour
  - mucinous/endometrioid or serous/endometrioid carcinoma: relatively frequent with the common epithelial subtypes (20–30% of cases) and each component at least 10% of the tumour area. The prognosis is often determined by the nature of the major component. However, the presence of a minor component of serous or undifferentiated carcinoma in an otherwise endometrioid adenocarcinoma adversely affects prognosis
  - endometrioid carcinoma with squamous differentiation (benign or malignant cytology).
— undifferentiated:
  - small cell carcinoma of either a. hypercalcaemic type (young, bilateral, small cells with follicle-like structures), or b. pulmonary-type (lung small cell carcinoma analogue), both of which are of poor prognosis and show variable EMA/cytokeratin positivity ± chromogranin. There is also a large cell neuroendocrine carcinoma variant
  - non-small cell: immunohistochemistry may be necessary to distinguish from malignant lymphoma, malignant melanoma, epithelioid variants of sarcoma, granulosa cell tumour and rare ovarian cancers, e.g. transitional cell carcinoma or squamous cell carcinoma
  - osteoclast-like
  - trophoblastic differentiation.

Malignant mixed mesodermal tumour (carcinosarcoma/sarcomatoid carcinoma)

— old age, poor prognosis, <1% of ovarian tumours.
— homologous: ovarian type carcinoma (serous, endometrioid, clear cell, undifferentiated) with cytokeratin positive spindle cells indicating variable malignant mesenchymal differentiation.
— heterologous: foci of immature/malignant cartilage, striated muscle, osteoid.

Sex cord/stromal

— 8% of ovarian neoplasms.
— thecoma-fibroma (85%): fibroma (storiform spindle cells/collagen stroma) is one of the commonest ovarian tumours. Thecomatous

elements are fat stain positive. Association with Meig's syndrome and endometrial hyperplasia. Sclerosing stromal tumour is a related variant. Fibrosarcoma is very rare.
— granulosa cell tumour (12%):
adult: micro-(macro)follicular (Call-Exner bodies), trabecular, insular, watered-silk, solid, sarcomatoid patterns and longitudinal nuclear grooves
juvenile: solid or cystic, follicular patterns of small cells ± mitoses. More aggressive than the adult counterpart.
— Sertoli-Leydig tumour: well/moderate/poor differentiation with varying proportions of tubules lined by Sertoli cells, Leydig cells and spindle cells ± heterologous elements, e.g. mucin secreting glands. Sertoli cells are keratin positive, stroma inhibin positive.
— mixed and unclassified variants (10% of cases).
— gynandroblastoma: equimixed android/gynaecoid elements, i.e. granulosa-theca/Sertoli-Leydig.
— gonadoblastoma: mixed germ cell/sex cord cell elements usually dysgerminoma/Sertoli/granulosa-like cells.
— sex cord tumour with annular tubules (SCTAT): Peutz-Jeghers syndrome; adenoma malignum cervix.
— the sex cord stromal tumours are variably inhibin/melan-A/calretinin/CAM5.2/CD99 positive but CA125/CK7 negative.

Steroid cell tumours
— rare (0.1%), hormonally active with virilization (75%).
— polygonal eosinophilic cells, inhibin positive.
— 30% are malignant based on size (>7 cm), mitoses, atypia, necrosis.

Germ cell tumours
— teratoma: mature/cystic
immature/solid
monodermal, e.g. carcinoid, struma ovarii (thyroid tissue)
malignant transformation, e.g. squamous carcinoma (80% of malignant cases), carcinoid tumour, adenocarcinoma, thyroid papillary carcinoma.
— dysgerminoma (seminoma analogue: PLAP/CD117 positive), yolk sac tumour (children/young adults, reticular/microcystic/papillary patterns, AFP positive, chemosensitive), embryonal carcinoma (CD30 positive).
— mixed germ cell tumour (8% of cases), e.g. dysgerminoma and yolk sac tumour.
— choriocarcinoma:
primary: rarely, primary prepubertal or as part of a mixed germ cell tumour
secondary: to gestational uterine, tubal or ovarian lesion (better prognosis).

Metastatic carcinoma

— 10–15% of malignant ovarian tumours often mimicking a primary lesion clinicopathologically: especially stomach, appendix, colorectum, pancreas, breast (infiltrating lobular).
— Krükenberg: classically bilateral signet ring cell metastases from stomach and mucin positive with a reactive fibrous ovarian stroma ± luteinization. Spread is peritoneal and differential diagnosis is primary ovarian signet ring cell carcinoma, ovarian goblet cell carcinoid, and sclerosing stromal tumour. Other sources for Krükenberg tumours are large bowel, appendix, gall bladder and breast.
— direct spread: colorectal carcinoma, carcinoma of fallopian tube, endometrium and cervix.
— distant spread: lung, malignant melanoma, breast, kidney, thyroid. Small cell ovarian tumours (juvenile granulosa, small cell ± hypercalcaemia) must be distinguished from metastatic small cell carcinoma of lung.

Features favouring an ovarian primary are unilaterality, large size with a smooth surface and an expansile growth pattern. Seventy percent of secondary carcinomas are bilateral. Other clues are solid, discrete, corticomedullary nodular deposits, surface deposits, prominent infiltrative stromal and lymphovascular invasion and lack of CK7 positivity. Prognosis of metastatic ovarian carcinoma is poor as this represents advanced disease. A number of metastases mimic primary ovarian carcinoma histologically, e.g. gut (endometrioid/mucinous), renal cell (mesonephroid/clear cell), thyroid (struma ovarii) and hepatocellular (yolk sac tumour) carcinomas. A relevant clinical history is crucial in designation and further clinical investigation, e.g. CT scan abdomen, serum AFP may be necessary to discover an occult primary lesion. See 8. Other pathology for further discussion.

3. DIFFERENTIATION

Adenocarcinoma

— well/moderate/poor/undifferentiated, or Grade 1/2/3/4.
— a provisional grading system for epithelial ovarian tumours of all histological types is based on the degree of glandular/papillary/solid differentiation, cellular pleomorphism and mitotic activity ± overt invasion of the stroma or capsule. The presence and extent of stromal invasion is a strong prognostic indicator.
— in serous carcinoma there is usually correlation between cytoarchitectural differentiation features, i.e. poorly differentiated tumours are solid with high nuclear grade vs. well to moderately differentiated with glands and papillae and lower nuclear grade. An exception to this is the grade 1 solid/nested psammomatous serous carcinoma.
— a suggested scheme for endometrioid carcinoma is similar to its uterine counterpart based on the percentage of non-squamous/non-morular solid growth pattern: grade 1 (≤5%), 2 (6–50%), 3 (>50%).

— in endometrioid and mucinous tumours disproportionate nuclear atypia raises the grade by one level e.g. 1 → 2. In serous, clear cell, transitional and squamous cell carcinomas the high nuclear grade takes precedence over architecture.
— in mucinous tumours the presence of invasion outweighs cytoarchitectural grading features.

Borderline (low malignant potential)
— serous lesions are of excellent prognosis regardless of stage and are bilateral in 20–25% occurring in a younger age group (40–50 years). They form 10–15% of epithelial tumours comprising epithelial complexity with budding, atypia, mitoses and nuclear layering (≤3 nuclei deep in mucinous lesions) but no destructive stromal invasion. Peritoneal recurrence in 10–15%. The outlook for mucinous borderline tumours depends on the subtype, i.e. endocervical (good) or intestinal (worse).

NB: micropapillary serous tumour/carcinoma requires no demonstrable invasion but is designated on the degree of micropapillary/cribriform epithelial complexity. It is an exophytic lesion often associated with invasive peritoneal implants, bilaterality and advanced stage and is of worse prognosis than usual serous borderline tumours.

Sex cord/stromal
— well/moderate/poor differentiation but weak correlation with prognosis and grading is more dependent on the specific tumour type.

Functional: e.g. oestrogenic drive to endometrium in thecoma (25% of cases), granulosa cell tumour; virilization in Sertoli-Leydig tumour.

Prognosis relates to size (< or >5 cm), an intact or deficient capsule, bulk of extraovarian disease, atypia, mitoses (per 10 hpfs), necrosis and bilaterality.

Recurrence (30%) tends to be local. It may be extrapelvic and after a considerable lag period of 10–20 years, although recurrent juvenile granulosa and Sertoli-Leydig tumours recur within 3 years. Raised serum inhibin levels may be useful in detecting recurrent granulosa cell tumour.

Germ cell
— mature: cystic (95% of cases). Common tissues are skin and appendage structures, muscle, fat, ganglia, glial tissue, respiratory, gastrointestinal and pancreatic glandular tissue, retinal elements, cartilage and bone.
— immature: solid with histologically identifiable immature tissues, especially cartilage, neuroepithelium, striated muscle, endodermal glands and immature cellular mesenchyme.
— grade 1: mostly mature tissue, loose mesenchyme, immature cartilage, focal (<1 low-power field/slide) immature neuroepithelium.
— grade 3: scant mature tissue, extensive (>3 low-power fields/slide) immature neuroepithelium ± peritoneal implants which can be

mature (e.g. gliomatosis peritonei) or immature, and are graded separately.
— ± carcinoma (e.g. squamous) or sarcoma (e.g. rhabdomyosarcoma, sarcoma of no specific type) in mature or immature lesions. An adverse indicator. 1–3% of cases.
— GFAP, synaptophysin can help in identification of immature neuroepithelial elements.
— combination chemotherapy for grade 2/3 tumours and those with peritoneal implants gives 90–100% survival.

4. EXTENT OF LOCAL TUMOUR SPREAD

Border: pushing/infiltrative.
Lymphocytic reaction: prominent/sparse.
Capsule/serosa/paratubal connective tissue/contiguous fallopian tube/uterus. Involvement of fallopian tube is usually secondary to primary ovarian disease wherein the bulk of tumour will usually reside. Note that extension of tumour along the tubal mucosa can sometimes mimic carcinoma in situ and a tubal origin. Spread to uterus is usually as a serosal plaque of friable tumour with invasion of outer myometrium and/or its underlying vessels.

Extensive sampling of ovarian epithelial cystic lesions is necessary (1 block/cm diameter) as there can be marked heterogeneity and coexistence of benign, borderline and malignant features, e.g. mucinous lesions. In this respect more blocks are required than in an obviously malignant homogeneous tumour and nodular/solid areas should be preferentially sampled in an otherwise cystic lesion. Microinvasion $\leq 10\,mm^2$ (or approximately 3 mm diameter) can be difficult to distinguish from crypt epithelial complexity and invagination into stroma (desmoplasia is a useful feature in carcinoma). It is occasionally seen in otherwise borderline serous tumours but does not alter the prognosis. Invasion >5 mm may help to discriminate between mucinous and endometrioid borderline and carcinoma lesions with a worse clinical outcome.

Invasion of stroma and/or capsule remains the hallmark of carcinoma but not infrequently its presence is difficult to assess or it is not evident. This is particularly problematic in mucinous lesions, where a designation of non-invasive carcinoma or intraepithelial carcinoma may be made on the basis of epithelial complexity with a confluent glandular pattern and cellular atypia alone, e.g. nuclear stratification ≥4 deep, cribriform epithelial pattern or stroma-free papillae of epithelial cells. Further sampling is necessary to exclude frankly invasive areas warranting the more usual designation of adenocarcinoma.

Minimal staging requires removal of the ovarian primary lesion, biopsy of the contralateral ovary, biopsy of omentum and peritoneal surfaces, and peritoneal washings for cytology if ascitic fluid is not present.

FIGO/TNM

The TNM classification applies to malignant surface epithelial-stromal tumours, including those of borderline malignancy. Non-epithelial

ovarian cancers may also be classified using this scheme. FIGO is based on surgical staging, TNM on clinical and/or pathological classification.

pT1 growth limited to the ovaries
- a. one ovary, capsule intact, no serosal disease or malignant cells in ascites or peritoneal washings
- b. two ovaries, capsule intact, no serosal disease or malignant cells in ascites or peritoneal washings
- c. one or both ovaries with any of: capsule rupture*, serosal disease or malignant cells in ascites or peritoneal washings.

pT2 growth involving one or both ovaries with pelvic tumour extension and/or implants
- a. uterus, and/or tube(s)
- b. other pelvic tissues
- c. 2a or 2b plus malignant cells in ascites or peritoneal washings

pT3 growth involving one or both ovaries with metastases to abdominal peritoneum†, and/or regional nodes
- a. microscopic peritoneal metastasis beyond pelvis
- b. macroscopic peritoneal metastasis ≤2 cm in greatest dimension beyond pelvis
- c. peritoneal metastasis >2 cm in greatest dimension and/or regional lymph node metastasis (N1)

pT4/M1 growth involving one or both ovaries with distant metastases, e.g. liver parenchyma or positive pleural fluid cytology.

The commonest pattern of spread is the contralateral ovary, peritoneum, para-aortic and pelvic lymph nodes and liver. Lung is the preferred extra-abdominal site and occasionally unusual sites, e.g. breast.

5. LYMPHOVASCULAR INVASION

Present/absent.
Intra-/extratumoral.
Look for particularly in paraovarian/paratubal connective tissues.

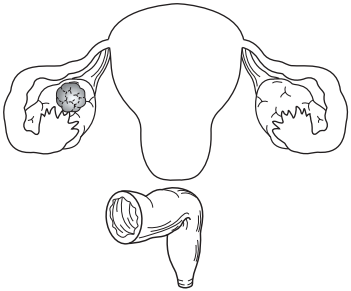
6. LYMPH NODES

Site/number/size/number involved/extracapsular spread.
Regional nodes: obturator (hypogastric), common iliac, external iliac, lateral sacral, para-aortic, inguinal. A regional lymphadenectomy will ordinarily include a minimum of 10 lymph nodes.

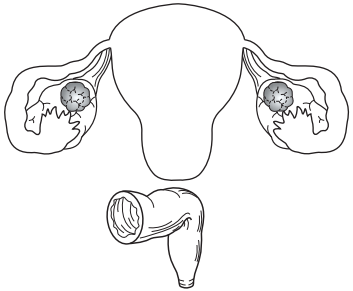
pN0 no regional lymph node metastasis

pN1 metastasis in regional lymph node(s).
- — beware of overcalling intranodal endosalpingiosis or Müllerian inclusions, which can be associated with borderline changes and difficult to distinguish from microscopic metastases. Comparison with the index ovarian lesion and disease elsewhere, e.g. peritoneum, is important in designation.

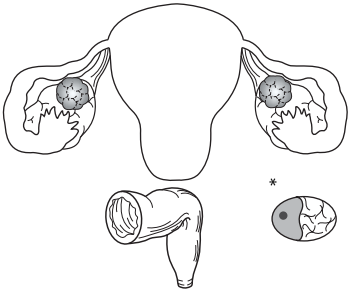
*Rupture of the capsule can be spontaneous or surgical.
†Peritoneal metastasis outside the pelvis includes involvement of the omentum.



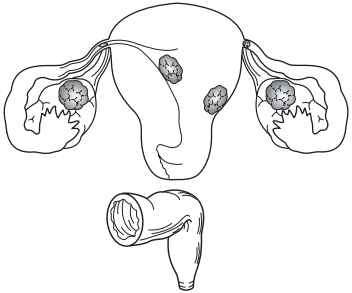
pT1a = confined to one ovary



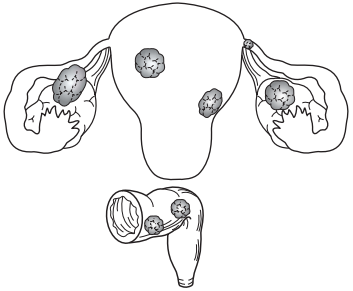
pT1b = confined to both ovaries



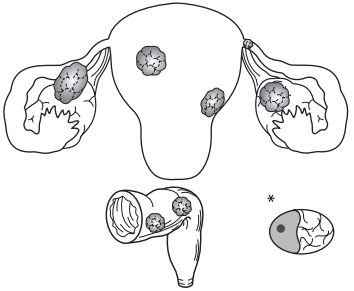
pT1c = confined to one or both ovaries with capsule rupture/serosal disease/malignant ascites or peritoneal washings*



pT2a = one or both ovaries with extension onto or into uterus and/or tube



pT2b = one or both ovaries with extension to other pelvic tissues



pT2c = pelvic extension (2a or 2b) plus malignant ascites or peritoneal washings*

FIGURE 23.1. Ovarian carcinoma.

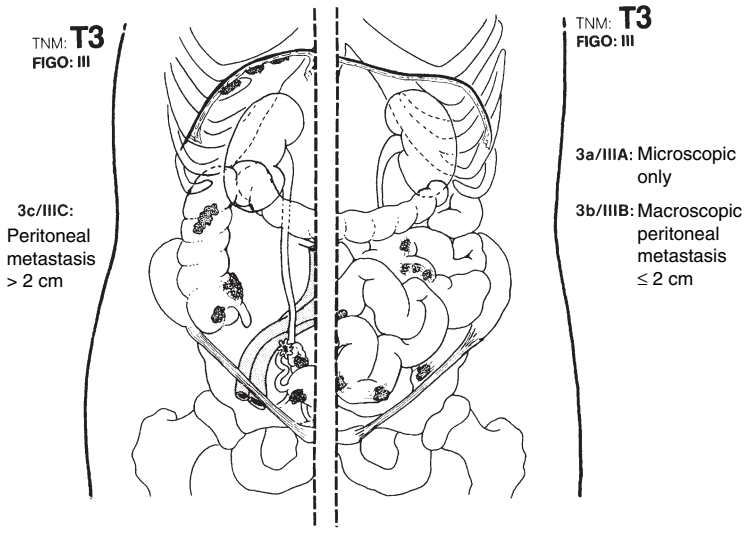


FIGURE 23.2. Ovarian carcinoma.

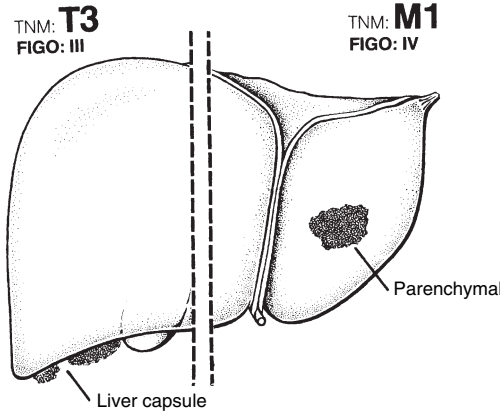


FIGURE 23.3. Ovarian carcinoma.

7. OMENTUM/PERITONEUM

Forty percent of serous borderline tumours, especially exophytic lesions, are associated with foci of peritoneal serous epithelial proliferation, particularly in the omental and pelvic peritoneum.

Endosalpingiosis

— no epithelial atypia: ±a benign or borderline ovarian lesion.
— a metaplastic process in serosal epithelial inclusions.

Implants

— epithelial atypia: +borderline ovarian serous lesion (rarely, mucinous).
The implants are assessed independently of the ovarian tumour as:
non-invasive or invasive (destructive infiltration of underlying tissue disrupting the omental lobular architecture), and epithelial (proliferative) or desmoplastic (stromal: >50–75% loose stroma/granulation tissue with small nests or papillae of epithelial cells).
Probably represent multifocal neoplasia arising in peritoneal inclusions. Endosalpingiosis, desmoplastic and non-invasive proliferating implants should be noted and follow-up recommended. Invasive proliferating implants should be regarded as low-grade carcinoma as they progress in 80% of cases with a 10-year survival of about 35%. Non-invasive proliferating implants are distinguished from surface serous carcinoma by greater epithelial architectural and nuclear atypia in >25% of the lesion area in carcinoma.

Pseudomyxoma peritonei

Pseudomyxoma peritonei is strongly associated with borderline ovarian mucinous lesions (of intestinal type) and/or concurrent appendiceal mucinous neoplasia. The peritoneal cavity fills with abundant mucin with or without a component of either cytologically bland, proliferating or malignant epithelium. Prognosis is poor as it is refractory to treatment, slowly progressive and leads to bowel obstruction. It arises due to either rupture or spread from an ovarian but more usually an appendiceal lesion. Appendiceal and ovarian lesions in pseudomyxoma coexist in 90% of cases and many of the latter are now considered to represent direct implantation from the former. Immunohistochemistry may be of help in that ovarian lesions of appendiceal origin may be CK20 positive/CK7 negative but primary ovarian tumours CK7 positive/CK20 negative. A CK20 positive/CK7 positive phenotype can indicate either origin as 50% of low-grade appendiceal mucinous neoplasms are of this immunophenotype and ovarian mucinous tumours can show patchy CK20 positivity. In this case consideration also has to be given to a metastasis from the pancreatico-biliary tree, which can also co-express CA125. In addition, comment should be made as to whether pseudomyxoma peritonei is free mucinous ascites, organizing mucin fluid or mucin dissection with fibrosis. The latter, abundant mucin in the peritoneal cavity, and the presence of epithelial cells in the mucin and atypical cytological appearances are also adverse prognostic parameters. Because of the strength of association, appendicectomy should be considered, particularly when mucinous ovarian tumours are bilateral and there is extra-ovarian peritoneal disease.

Primary peritoneal carcinoma

— young to middle-age females.
— serous adenocarcinoma in type (CK7/WT1/ER positive).
— extensive peritoneal disease ± an ovarian serosal component with otherwise normal ovaries (any ovarian invasion <5 mm^2).

— treated by surgical cytoreduction and chemotherapy. The psammomatous-rich carcinoma variant has a better prognosis and indolent course.

Metastatic adenocarcinoma

— from primary ovarian carcinoma, usually forms either macroscopically obvious confluent tumour nodules or a diffusely thickened omental cake.

8. OTHER PATHOLOGY

Hereditary factors are responsible for 5–10% of ovarian carcinoma. Mutations in the BRCA1 and BRCA2 genes carry a 20–50% risk of ovarian cancer up to the age of 70 years. The tumours occur 5 years earlier than sporadic ovarian carcinoma, are mainly of serous histological type, have a strong association with breast cancer (BRCA1: 87% risk) and to a lesser extent (9% risk) hereditary non-polyposis colorectal cancer. Prognosis is similar to that of sporadic ovarian carcinoma. Lesions may be early or microscopic and require serially slicing and processing in toto of both ovaries and fallopian tubes.

— Meig's syndrome: ascites, ovarian fibroma and right sided pleural effusion.
— Contralateral ovary and tube: synchronous/metastatic disease of parenchyma or serosa (e.g. serous papillary lesions—40%). Clues to metastatic disease in the non-dominant ovary are multiple nodules, surface implants and lymphovascular invasion. Synchronous primary lesions will tend to show similar tumour distribution and appearance, e.g. size and cystic with solid components.
— Uterus: synchronous/metastatic disease of endometrium, endocervix or serosa (e.g. endometrioid carcinoma) i.e. multifocal Müllerian neoplasia. When tumour is present in the ovary and endometrium (usually endometrioid carcinoma, sometimes serous carcinoma) it can be difficult to tell which is the primary/metastatic site or if they are independent primary tumours, i.e. stage I disease. The tumour site and distribution (dominant bulk/depth of invasion/multiple serosal nodules/lymphovascular invasion) and evidence of any precancerous lesions (endometrial hyperplasia/ovarian endometriosis) are useful clues. The good prognosis of endometrioid carcinomas confined to the endometrium and one or both ovaries suggests that they usually represent independent synchronous tumours but in other cases with extensive disease distinction can be somewhat arbitrary and best attributed in light of full clinicopathological details. Ovarian carcinoma metastasising to endometrium is rare.

Concurrent ovarian endometriosis (± atypical hyperplasia) and endometrial carcinoma are seen in up to 25% of ovarian endometrioid adenocarcinomas. The frequency of associated disease is lower in ovarian clear cell (mesonephroid) carcinoma, which may also be related to foci of ovarian endometriosis (10–20%), with the latter now considered in some cases to be a potentially premalignant lesion. Clear cell carcinoma

should be distinguished from yolk sac tumour, dysgerminoma and metastatic renal cell carcinoma (see below).

DNA aneuploidy in borderline ovarian epithelial lesions and ovarian adenocarcinoma is generally regarded as an adverse prognostic indicator. Mucinous borderline tumours are intestinal (85% of cases ± associated with pseudomyxoma peritonei) or Müllerian (endocervical; 30% are associated with endometriosis) in type with differing pathological and clinical features representing high and low-grade proliferating mucinous tumours, respectively. A wide spectrum of benign/borderline/malignant intestinal differentiation can be seen and metastases from appendix, stomach, pancreas and colon need to be excluded clinically, with primary ovarian lesions now recognized as comprising a minority of ovarian mucinous tumours of borderline or malignant character. Mucinous tumours can also rarely show a spectrum of mural nodules of varying size and appearances ranging from anaplastic carcinoma (cytokeratin positive large/spindle cells: aggressive) and sarcoma (fibrosarcoma, rhabdomyosarcoma) to benign behaving sarcoma-like lesions with cytokeratin negative giant cells and spindle cells. Pseudomyxoma ovarii is commoner in borderline and malignant lesions, particularly those with pseudomyxoma peritonei.

Mucinous (intestinal type) and endometrioid ovarian carcinomas and Sertoli-Leydig tumours can closely mimic or be imitated by colorectal and other gut adenocarcinomas. These secondaries can occur after, concurrently or even predate the detection of the primary tumour.

Immunophenotype

Colorectal metastases to the ovary tend to be bilateral, solid with areas of necrosis, and show crescentic garland-type strips of tumour with segmental and dirty necrosis on microscopy. There is diffuse cellular staining with CEA, CA19-9 and β-catenin and CA125 is usually negative. Ovarian carcinomas tend to be cystic with solid areas, uni- or bilateral, show cell apex CEA staining, ±CA125 and variable CA19-9. β-catenin is negative but CDX-2 can be positive, making it unsuitable for distinction from colorectal cancer. Mucin is scanty in endometrioid variants and negative in Sertoli-Leydig tumours. Anatomical distribution of disease is important and commonly the rectosigmoid primary will also show locoregional mesenteric nodal disease and peritoneal involvement. At frozen section the site of origin of a mucinous carcinoma can not be reliably given, whereas this distinction can be made for ovarian serous or clear cell carcinoma invading large bowel. Despite this the differential diagnosis between ovarian and colorectal cancer can still be difficult and in any ovarian mucinous or endometrioid tumour the possibility of a gastrointestinal origin must be excluded clinically. Differential cytokeratin expression can be of use with intestinal tumours showing a different profile (cytokeratin 20 positive/7 negative) from ovarian tumours (cytokeratin 7 positive/20±, patchy). Gut cancers are usually p53 positive. Note that gastric, pancreatic and biliary cancers are also variably cytokeratin 7/20 positive and may even express CA125, as do some endometrial

cancers. Metastatic breast carcinoma shows a similar cytokeratin profile (CK7+/CK20–, ER/PR positive) but also GCDFP-15 positive. Infiltrating lobular breast cancer is particularly prone to gynaecological tract metastasis and a relevant clinical history is important. Other metastatic tumours mimicking primary ovarian cancer are renal cell carcinoma (CT abdomen, sinusoidal vascular pattern, less hob-nail cells, RCC ab/CD10/vimentin positive) and transitional cell carcinoma of the urinary tract (uroplakin III/ CK7/CK20 positive). In peritoneal fluid cytology specimens BerEP4 is helpful in distinguishing between mesothelial and epithelial cells.

Serum levels and tissue expression of various antigens are detectable in a range of ovarian neoplasms but characteristically strong associations are:

CA125/WT-1	ovarian carcinoma (serous type)
AFP	ovarian yolk sac tumour, immature teratoma
βHCG	ovarian choriocarcinoma, immature teratoma
inhibin, CD99	granulosa cell tumour
HPL/PLAP	dysgerminoma.

Prognosis

Prognosis of ovarian carcinoma relates to morphological features such as histological type and grade, volume percentage epithelium and mitotic activity index as well as large volume of disease after cytoreduction, high-volume ascites and high postoperative CA125 levels. Overexpression of markers such as p53 and Her-2 may also be adverse but the predominant factor is stage of disease with the degree of extraovarian spread and omental involvement. Early stage disease confined to the ovary or pelvis has a 5-year survival rate of 80%, whereas the majority (70%) of patients present late with widespread metastatic disease and 10–20% survival at 5 years. Undoubtedly there are different types of ovarian adenocarcinoma according to their origins and behaviour—e.g. low grade cystadenocarcinoma arising from a cystic ovarian neoplasm, or high grade adenocarcinoma arising from a thin rim of outer cortex and showing aggressive behaviour with disproportionately extensive local spread and involvement of adjacent structures. Overall survival probability at 5 years is about 35–40%. Serum CA125 levels are useful for monitoring disease progression and response to treatment but will be elevated in only 50% of early, curable disease. A suggested screening strategy is a combination of clinical examination, serum CA125 levels and abdominopelvic ultrasound examination. FNAC has a role to play in the distinction between functional (e.g. granulosa/luteal-inhibin positive) cysts and benign or malignant epithelial (cytokeratin/BerEp4 positive) lesions. Accurate surgical assessment is needed to avoid understaging of ovarian cancer, with surgical excision the mainstay of treatment. Cytoreductive surgery is also used for extensive disease with adjuvant therapy. In some cases subsequent "second-look" operation is carried out to assess the response to therapy and as a prequel to further chemotherapy. Borderline serous and endocervical mucinous ovarian epithelial neoplasms are uniformly of

excellent prognosis (95–100% 5-year survival), even if microinvasion (<1–3 mm diameter) is present, with uni- or bilateral adnexectomy as effective as radical surgery. Prognosis is worse with invasive peritoneal implants and poor for intestinal-type borderline mucinous lesions associated with pseudomyxoma peritonei. Stage I mucinous adenocarcinoma has a good prognosis but may metastasize if extensive stromal invasion is present. The possibility of an ovarian mucinous tumour representing spread from appendix, colorectum or pancreaticobiliary tree should always be considered. Clear cell carcinoma has a worse outlook than the other usual types of ovarian cancer, e.g. 5-year survival 70% for stage I disease. Undifferentiated carcinoma and malignant mixed mesodermal tumour (carcinosarcoma) have a poor prognosis. The vast majority of sex cord/stromal tumours are stage I with 85–95% 5-year survival. Higher stage and tumour rupture are adverse indicators but only about 10–30% subsequently recur. Malignant ovarian germ cell tumours are unusual and occur mainly in children, adolescents and young adults. 60% present with stage I disease (5-year survival 90%) with a 5-year survival rate of 70–80% for all stages of disease. Serum βHCG and AFP levels are useful in postoperative monitoring and postoperative chemotherapy is used for tumours other than stage I, grade I immature teratoma.

9. OTHER MALIGNANCY

Lymphoma

— primary or more commonly secondary to systemic disease, particularly if low-grade B-cell lymphoma.
  Burkitt's/Burkitt's-like: childhood, young adults, associated with bilateral breast lymphoma in young women.
  non-Hodgkin's: diffuse large B cell, average survival 3 years, often shows sclerosis.
— differential diagnoses: includes the full range of malignant small blue cell tumours as well as granulosa cell tumour and dysgerminoma. Confirm by immunohistochemistry for lymphoid markers and negativity for inhibin, PLAP, desmin, CD99 and neurofilament/synaptophysin/chromogranin.

Leukaemia

— granulocytic sarcoma (CD68/chloroacetate esterase/myeloperoxidase positive).
— 10–20% of acute and chronic leukaemias; site of relapse for ALL during bone marrow remission.

Sarcoma

— leiomyo-/rhabdo-/angio-/chondro-/osteo-/neurofibro-sarcoma: all rare and more often part of a malignant mixed mesodermal tumour or (immature) teratoma.
— endometrioid stromal sarcoma: granulosa-like cells with distinctive vascular pattern of spiral arteriole-type vessels. CD10 positive/inhibin negative/smooth muscle actin/desmin focal. Exclude spread from a uterine lesion.

— undifferentiated (high-grade) sarcoma: fibro-/rhabdomyosarcoma-like with atypia and mitoses.

Malignant melanoma

— secondary: present in 20% of fatal cases.
— primary: within the wall of a dermoid cyst.

Secondary involvement by peritoneal mesothelioma (well-differentiated papillary/multicystic or of no specific types), intra-abdominal desmoplastic small round cell tumour (with divergent differentiation; cytokeratin, EMA, vimentin, desmin positive; pelvis and abdomen of young people), Ewing's sarcoma/PNET, neuroblastoma (neurofilament/synaptophysin) and rhabdomyosarcoma (desmin/myo D1/myogenin).

10. COMMENTS ON FALLOPIAN TUBE CARCINOMA

Primary carcinoma of the fallopian tube is rare (<1% of primary genital tract malignancy: increased in BRCA1/BRCA2 gene mutations) and greatly outnumbered by direct tubal extension from ovarian carcinoma (where the bulk of tumour is in the ovary) and uterine carcinoma (where the bulk of tumour is in the uterus). The tumour should be located macroscopically within the tube or its fimbriated end, and the uterus and ovaries should be grossly normal with any malignancy conforming to features of metastases or, alternatively, in keeping with the size and distribution of an independent primary. In primary fallopian tube carcinoma the tube is distended by a solid or papillary tumour and histologically the cancer is invasive papillary adenocarcinoma usually similar to ovarian serous papillary carcinoma. However, the full spectrum of Müllerian subtypes has been reported, e.g. endometrioid, mucinous, clear cell, transitional and unusual tumours, e.g. squamous cell carcinoma. Prognosis depends mostly on the stage of disease, with 5-year survival rates of 77% for stage I and 20% for stage III. Tumour recurrence is intra-abdominal and spread is similar to that of ovarian carcinoma. Other rare malignant tumours recorded are malignant mixed mesodermal tumour, leiomyosarcoma and gestational choriocarcinoma. Benign adenomatoid tumour is the commonest neoplasm, occurring within the wall usually near the uterine cornu.

Broad ligament lesions include female Wolffian adnexal tumour (solid, sieve like trabecular/tubular pattern and CK7/inhibin/calretinin/androgen receptor positive, benign) and cystic lesions lined by Müllerian epithelium of variable type (e.g. serous, mucinous etc) and character (usually benign/occasionally borderline or malignant).

FIGO/TNM

For details see ovarian carcinoma.

pT1 tumour limited to the fallopian tube(s)
pT2 tumour involving tube(s) with pelvic extension
pT3 tumour involving tube(s) with metastases to abdominal peritoneum, and/or regional nodes
pT4 tumour involving tube(s) with distant metastases, e.g. liver parenchyma or positive pleural fluid cytology.

24
Endometrial Carcinoma

1. GROSS DESCRIPTION

Specimen

— curettage/pipelle sample (on an outpatient basis: some cases are also detected by routine cervical smear).
— subtotal/total/radical hysterectomy/bilateral salpingo-oophorectomy/limited pelvic node dissection.
— size (cm) and weight (g).
— suboptimal fixation of the endometrium in a hysterectomy specimen can make accurate histological assessment problematic and this can be countered by post-surgical injection of formalin with a needle through the cervical os.
— most endometrial cancers present with abnormal vaginal bleeding and this is particularly significant in a postmenopausal patient. Investigation is by outpatient pipelle endometrial sampling and the retrieved fragments are usually very scanty and may require filtering from the formalin fixative. The role of the pathologist is not to phase the endometrium but to comment on whether any functional endometrium is actually represented and, if so, if it is benign, atypical or malignant. Atypical endometrium may represent a false-negative sample of a concurrent adenocarcinoma. Investigation also includes transvaginal ultrasound scan which can relate endometrial thickness to the menopausal status (postmenopausal usually <5 mm) and detect any focal lesions, e.g. polyps. Hysteroscopy allows direct visualization of the uterine cavity and more extensive sampling. Transcervical resection of the endometrium is reserved for benign dysfunctional endometrium. If there are histological features suspicious of or diagnostic of malignancy in biopsy material, MRI scan is used to assess tumour stage, in particular, the depth of myometrial invasion and the presence of cervical or extrauterine involvement. CT scan assesses more distant spread. Treatment of uterine cancers (carcinoma, sarcoma, carcinosarcoma) is by hysterectomy and bilateral salpingo-oophorectomy with peritoneal washings as part of the staging procedure. Modified radical hysterectomy (inclusive of vaginal cuff, parametria and limited regional lymphadenectomy) is considered for deeply invasive cancers, those with cervical involve-

ment or high-grade cancers (serous, clear cell, undifferentiated, squamous). They may also require post-operative chemoradiotherapy. Occasional locally advanced tumours are not amenable to resection and chemo-/radiotherapy is used as the first line of management.

Tumour

Site
— fundus, body, isthmus. Involvement of the lower uterine segment is unfavourable.

Size
— length × width × depth (cm) or maximum dimension (cm).

Appearance
— polypoid/papillary/solid/ulcerated/necrotic/haemorrhagic.
— malignant mixed mesodermal tumours are typically fundal and polypoid in an elderly patient and may protrude inferiorly through the internal cervical os.

Edge
— circumscribed/irregular.

Extent
— infiltration endometrium, myometrium, serosa, cervix.

Adjacent endometrium
— atrophic, hyperplastic, polypoid.

2. HISTOLOGICAL TYPE

The vast majority are adenocarcinoma of two main types although there is overlap between the categories:

— type I (prototype: endometrioid adenocarcinoma): peri-/postmenopausal, low parity, high socio-economic status, obesity, diabetes, hypertension, hyperoestrogenism (hormonal therapy or secreting tumour, e.g. ovarian sex cord-stromal), background endometrial hyperplasia. Microsatellite instability/PTEN mutations.
— type II (prototypes: serous and clear cell carcinoma): older patients, more aggressive, atrophic endometrium with precursor EIC (endometrial intraepithelial carcinoma). p53 mutations.

A minority of endometrial cancers are familial or associated with hereditary non-polyposis colorectal cancer. Cumulative dose of tamoxifen is also a risk factor.

Endometrioid adenocarcinoma
— 70–80% of cases.
— typical: low-grade well differentiated endometrial-type glandular pattern, perimenopausal, due to unopposed oestrogenic drive ± adjacent endometrial hyperplasia.

— variants:
  - with squamous differentiation—up to 30% of cases. The tumour is graded on the glandular component as it can be difficult to tell if the squamous element is benign or malignant. Where both elements are well differentiated the designation adenocanthoma is sometimes used
  - secretory carcinoma—cells resemble secretory endometrium
  - ciliated carcinoma—rare, cells resemble tubal epithelium
  - villoglandular carcinoma—low-grade, well differentiated and papillary. Exclude high-grade serous carcinoma (high-grade nuclear characteristics with a tufted papillary pattern)
  - Sertoliform carcinoma.

Serous (papillary) adenocarcinoma
— 5–10% of cases.
— high grade in the elderly and de novo with no adjacent hyperplasia but associated with EIC.
— lymphovascular/myometrial invasion and omental spread often disproportionate to the amount of endometrial disease.
— potentially multifocal with extrauterine lesions, e.g. ovary, tube.
— high-grade nuclear characteristics, usually a papillary pattern but occasionally tubuloglandular.
— necrosis and psammoma bodies are often seen. Overexpresses p53 and Ki-67/ER±/PR–/PTEN–. Also WT-1 negative in distinction from ovarian papillary serous carcinoma, which is positive.
— poor prognosis, 30% 5-year survival.

Clear cell adenocarcinoma
— 1–5% of cases; postmenopausal. Not related to diethylstilboestrol and aggressive with myometrial invasion.
— >50% of the cells are clear cell, mixed solid/glandular/tubulocystic/papillary architecture.

Mucinous adenocarcinoma
— >50% cells have stainable mucin.
— usually low grade, minimally invasive and good prognosis.
— distinguish from cervical adenocarcinoma by differential biopsy/curettage and exclude a gastrointestinal primary (clinical history, CK20 positive/CK7 negative).

Squamous cell carcinoma
— old age often with cervical stenosis and pyometra; exclude spread from cervical carcinoma.

Mixed
— second component: >10% e.g. composite endometrioid/serous/clear cell. Any carcinoma with >25% serous characteristics tends to behave more aggressively and should be designated as such. Adenocarcinoma with squamous differentiation is excluded. Adenosquamous carcinoma (where both components are obviously malignant) is a mixed lesion with a poor prognosis.

Undifferentiated carcinoma
— small cell/not otherwise specified: aggressive.
— cervical primary and lung primary must be excluded in small cell carcinoma.

Malignant mixed Müllerian tumours (MMMT)
— low-grade malignancy: adenosarcoma; carcinofibroma.
— high-grade malignancy: carcinosarcoma/sarcomatoid carcinoma comprising endometrial adenocarcinoma with a biphasic pattern and vimentin/cytokeratin positive malignant spindle cells. Lesions can be either homologous or heterologous (containing tissues alien to the uterus, commonly immature/malignant cartilage, striated muscle, bone). Carcinosarcoma is the commonest malignant mixed tumour and 50% contain heterologous elements (see 8. Other pathology for further discussion).

Metastatic carcinoma
— direct spread: cervix, ovary, bladder, rectum.
— distant spread: infiltrating lobular breast carcinoma, kidney, malignant melanoma, stomach, pancreas. The commonest are breast, stomach, colon, pancreas. Often myometrial with an endometrial component, metastases can mimic primary endometrial disease, e.g. infiltrating lobular breast carcinoma (endometrial stromal sarcoma), renal carcinoma (clear cell carcinoma) and colorectal carcinoma (mucinous carcinoma). A relevant clinical history and comparison with previous histology are crucial in making the distinction and metastases should be considered in any endometrial cancer of unusual appearance, multinodular growth pattern, prominent lymphovascular involvement and lack of precancerous endometrial changes.

3. DIFFERENTIATION
Well/moderate/poor/undifferentiated.
— 80–85% are well to moderately differentiated.
Grade I/II/III for endometrioid adenocarcinoma.

The glandular component of endometrioid adenocarcinomas is graded I <5%, II 6–50%, and III >50% non-squamous, non-morular solid growth pattern. Nuclear grading can also raise the architectural grade, e.g. II→III: grade 1 (oval nuclei, even chromatin, inconspicuous nucleolus, few mitoses) and grade 3 (irregular, rounded nuclei, prominent nucleoli, frequent mitoses). Grade 2 nuclear grade is intermediate between grades 1 and 3. In tumours with squamous differentiation grading is based on the glandular component. Serous, clear cell and undifferentiated carcinomas are considered high grade with nuclear grade taking precedence over architecture. Mucinous carcinomas are generally grade 1.

4. EXTENT OF LOCAL TUMOUR SPREAD
Border: pushing/infiltrative.
Lymphocytic reaction: prominent/sparse.

Endometrium

— EIN (endometrial intraepithelial neoplasia) is an umbrella term encompassing and highlighting the diagnostic difficulties there are in distinguishing between entities on the overlap spectrum of complex endometrial hyperplasia with atypia and intra-endometrial adenocarcinoma (pT1a). Progression along the spectrum is characterized by increased glandular crowding and cytological atypia with reduction in intervening stroma. An important differential diagnosis is a benign mimic with focal glandular crowding, e.g. endometrial polyp (look for covering epithelium and prominent vascular stroma with thick-walled vessels).
— EIC (endometrial intraepithelial carcinoma) is effectively carcinoma in situ of the endometrial surface epithelium and is present adjacent to or overlying 90% of serous carcinomas. It overexpresses p53 and Ki-67. It is also occasionally seen with clear cell carcinoma and even extrauterine peritoneal disease in the absence of invasive endometrial cancer.

Myometrium

— proportion of wall involved <50%, >50%.
— if >50% on MRI scan a radical hysterectomy is considered.

Extent of myometrial invasion relates to the histological type and grade of carcinoma. True myometrial invasion must be distinguished from expansion of the endo-/myometrial junction (look for a continuous line of myometrial vascular structures in a compressed atrophic myometrium) and abnormal epithelium in pre-existing adenomyosis (look for periglandular endometrial stroma-CD10 positive). Invasive stromal desmoplasia and inflammation are useful diagnostic clues although often not present in carcinoma. Endometriosis and endometrial–myometrial junction containing carcinoma usually have a broad front and smooth outline.

Serosa

— distance (mm) of the deepest point of invasion from the nearest serosal surface.

Endocervix/exocervix

— 10% of cases usually by direct invasion, lymphatic spread or occasionally by implantation following curettage. Distinction between an endometrial and cervical origin can be difficult clinically and histologically in curettage samples. Some reliance is placed on the nature of the tissue from which the carcinoma appears to be arising, e.g. normal or neoplastic cervix, or hyperplastic endometrium. Immunohistochemistry may also be of help in that endometrioid adenocarcinoma is usually vimentin/ER positive and CEA negative while cervical adenocarcinoma is the opposite of this. p16 antibody also stains more strongly in cervical adenocarcinoma.

Fallopian tubes/ovaries

Omentum

FIGO/TNM

The FIGO stages are based on surgical staging.
TNM stages are based on clinical and/or pathological classification and apply to carcinomas and malignant mixed mesodermal tumours.

pTis carcinoma in situ
pT1 tumour confined to the corpus:
  a. limited to the endometrium
  b. invades up to or less than half of myometrium
  c. invades more than half of myometrium
pT2 tumour invades corpus and cervix:
  a. endocervical glands only
  b. cervical stroma
pT3 outside the uterus but not outside the true pelvis:
  a. serosa and/or adnexae (direct extension or metastasis), and/or malignant cells in ascites/peritoneal washings
  b. vaginal disease (direct extension or metastasis)
pT4 extends outside the true pelvis or has obviously involved* the mucosa of the bladder or bowel.

Invasion of the parametria is pT3a. "Frozen pelvis" is a clinical term meaning tumour extension to the pelvic wall(s) i.e. T3b.

5. LYMPHOVASCULAR INVASION

Present/absent.
Intra-/extratumoral.
— particularly serous carcinoma.

6. LYMPH NODES

Site/number/size/number involved/extracapsular spread.
Regional nodes: pelvic (obturator and internal iliac), common and external iliac, parametrial, sacral and para-aortic. A regional lymphadenectomy will ordinarily include a minimum of 10 lymph nodes.

pN0 no regional lymph nodes metastasis
pN1 metastases in regional lymph node(s).

The commonest sites of extrauterine spread are the regional nodes and ovaries. Nodal disease relates to the tumour grade, type, depth of invasion and lymphovascular involvement. Invasion of the outer third of the myometrium is associated with nodal metastasis in up to 33% of cases. Recurrences are in the pelvis and vaginal vault. Distant metastases go to lung, liver, bone, CNS and skin of the scalp.

7. EXCISION MARGINS

Distances (mm) to the serosa, tubal and inferior vaginal limits.

*Requires histological confirmation by biopsy. Invasion of the rectal wall or bladder wall is pT3.

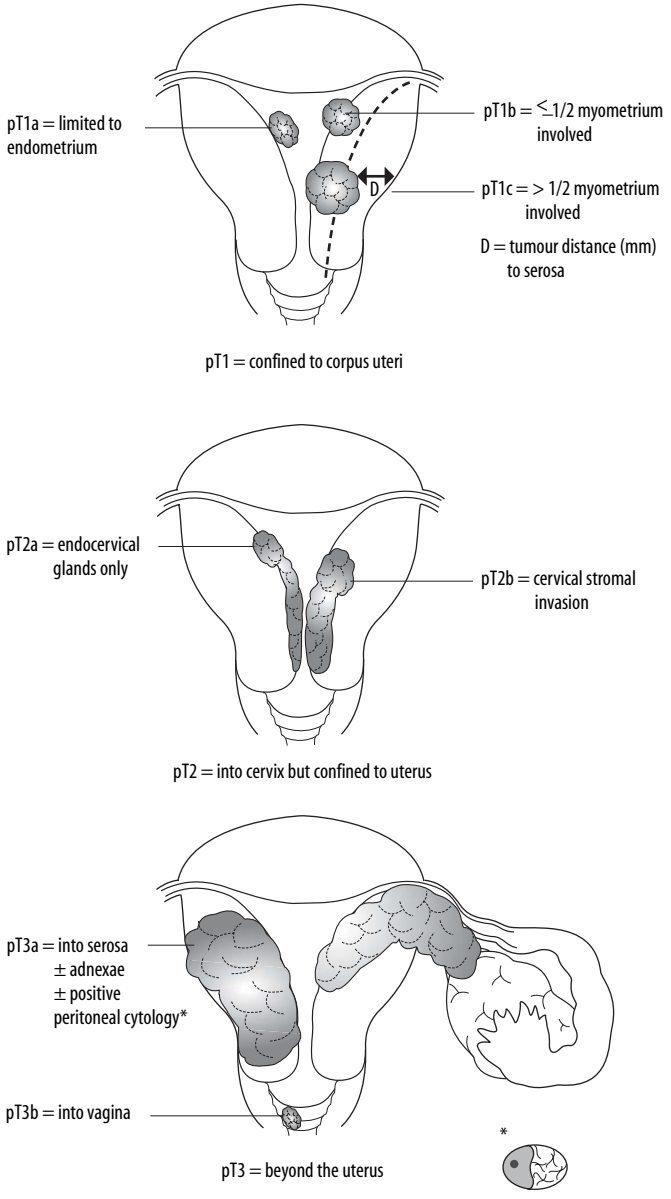


FIGURE 24.1. Uterine carcinoma.

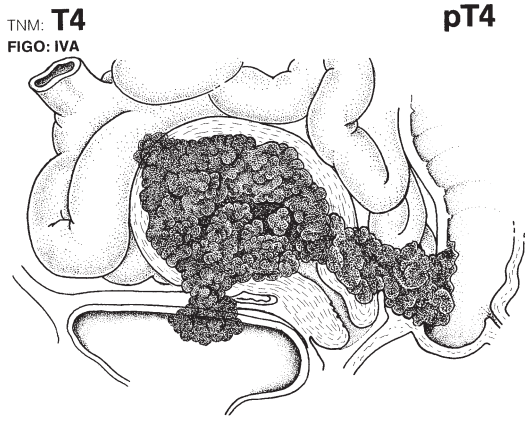


FIGURE 24.2. Uterine carcinoma.

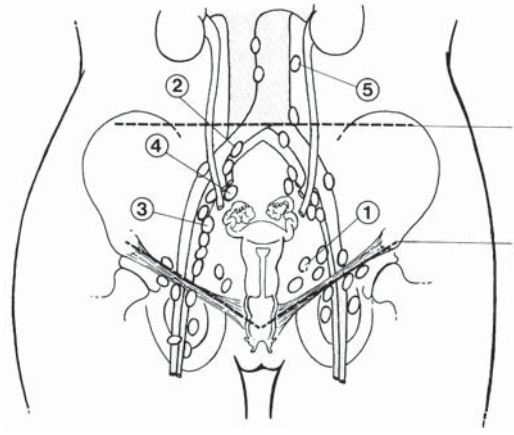


FIGURE 24.3. Uterine carcinoma: regional lymph nodes.

8. OTHER PATHOLOGY

Uterus

— polyp(s), hyperplasia (simple or complex with architectural ± cytological atypia), adenomyosis.

Carcinoma only rarely develops within a preexisting endometrial polyp although this is increased in tamoxifen therapy.

Twenty-five percent of untreated atypical hyperplasias progress to adenocarcinoma and up to 40% are associated with concurrent disease.

Features favouring adenocarcinoma over complex hyperplasia with cytological atypia are: intraglandular epithelial bridges, intraglandular polymorphs and necrosis, cytological atypia, mitoses and stromal invasion. Criteria for stromal invasion include: a. irregularly infiltrating glands associated with a fibroblastic or desmoplastic response, and/or b. extensive papillary or confluent glandular (cribriform) growth patterns. Stromal and superficial myometrial invasion are useful in distinguishing between intraendometrial and invasive adenocarcinoma in curettage specimens.

Ovary

— thecoma, granulosa cell tumour, endometrioid carcinoma, endometriosis.

Accompanying ovarian carcinoma is seen in 5–10% of endometrial carcinomas. Distinction between synchronous primary lesions and ovarian secondaries rests on the latter being bilateral, multinodular, often serosal and with ovarian stromal lymphovascular invasion. There is a higher frequency of concurrent primaries in endometrioid carcinoma of ovary (25%).

Tamoxifen-related polyps, hyperplasia, adenocarcinoma, adenosarcoma, carcinosarcoma (MMMT): tamoxifen is an anti-oestrogen but has paradoxical oestrogenic effects on the endometrium leading to an increased frequency of a range of endometrial neoplasms, some of which are prognostically adverse. Polyps can be large, multiple, necrotic, have areas of glandular, papillary or clear cell metaplasia and may even harbour carcinoma.

Carcinosarcoma/sarcomatoid carcinoma is often polypoid at the fundus of an elderly patient with lymphovascular invasion and 30% present with stage III/IV disease. The carcinomatous component is usually high-grade glandular (endometrioid, clear cell, serous or undifferentiated) and the sarcomatous element homologous (cf. endometrial stroma, leiomyosarcoma, fibrosarcoma) or heterologous (striated muscle, cartilage, bone, fat). Immunohistochemistry for epithelial and mesenchymal markers, e.g. desmin, may be necessary to confirm the diagnosis. Five-year survival is 20–40% in this aggressive neoplasm.

The majority (80%) of adenosarcomas arise in the postmenopausal endometrium. They are polypoid with proliferative type glands and usually homologous stromal type sarcoma distributed in a condensed periglandular cambium layer. Recurrence (30%) relates to mitoses, stromal overgrowth and myoinvasion in this low- to intermediate-grade malignancy.

Immunophenotype

Endometrial carcinoma usually co-expresses cytokeratins (7, 8, 18, 19) and vimentin. Oestrogen and progesterone marking is common related to histological grade and is of some use in assessing potential response to hormonal therapy in disseminated disease. CEA stains weaker than in

cervical carcinoma. High-grade serous carcinomas overexpress p53 and Ki-67 and in contrast to endometrioid carcinomas are often negative for ER/PR and PTEN. These immunoprofiles may be of use in distinguishing high nuclear grade endometrioid carcinoma from serous carcinoma with a tubuloglandular pattern. DNA aneuploidy is an index of high-grade, advanced-stage tumours and overexpression of Ki-67, p53 and Her-2 (20–40% of cases) is adverse.

Prognosis

Radical hysterectomy is considered for endometrial carcinoma if there is >50% myometrial invasion with grade II or III histology, invasion of the cervix, undifferentiated, clear cell or serous carcinoma, lymphovascular invasion or suspicious nodes on CT scan. Preoperative adjuvant chemo-/radiotherapy may also be used in these circumstances. Intraoperative frozen section of suspect nodes is an important prequel to radical resection and, if positive, a more conservative approach adopted.

Overall 5-year survival for endometrial carcinoma is 80–85% with type I oestrogen-related cases arising from a background of hyperplasia doing better than type II non-oestrogen-dependent lesions (30–70% 5-year survival). Serous, undifferentiated, squamous and clear cell carcinomas are more aggressive than equivalent stage endometrioid tumours. Lymphovascular invasion, which correlates with progressing tumour grade, myometrial invasion and stage (cervical and extrauterine spread), is an adverse prognostic factor (70–75% 5-year survival). Prognosis also relates strongly to tumour stage: I, 82–95% 5-year survival; II, 60–80%; III, 30–50%. Grade I tumours (87% 5-year survival) fare better than grade III cancers (58% 5-year survival).

9. OTHER MALIGNANCY

Endometrial stromal lesions can be benign (stromal nodule) or malignant, the latter having infiltrating margins. Curettings impose limitations in making this assessment, which is more appropriately done on a hysterectomy specimen.

Endometrial stromal sarcoma

— low-grade malignancy resembling endometrial stroma (stromal cells/spiral arteriole vascular pattern) with infiltrative margins and variable mitoses (usually <5–10/10 hpfs). Characteristic lymphovascular invasion (previously called endolymphatic stromal myosis). Prone to local pelvic or abdominal recurrence (30%) after many years have elapsed and may cause pressure effects, e.g. hydronephrosis. Sometimes hormone responsive to adjuvant progesterone therapy.

Undifferentiated uterine sarcoma

— previously high-grade stromal sarcoma. Pleomorphism and mitoses (>10/10 hpfs) with infiltrating margins and aggressive behaviour (50% 5 year survival). Size of tumour (>4 cm) and extrauterine extension are adverse indicators in low- and high-grade lesions. Treatment is

surgical although there is some evidence for partial response to chemotherapy and hormonal manipulation in metastatic disease.

Stage:

I tumour confined to the uterine corpus
II tumour confined to the corpus and cervix
III extrauterine pelvic extension
IV extrapelvic extension.

Endometrial stromal sarcomas are CD10 and vimentin positive ± patchy actin/desmin and low-grade lesions preserve a pericellular reticulin pattern. Differential diagnosis is undifferentiated carcinoma (cytokeratin, EMA positive) and leiomyomatous tumour (strongly desmin/h-caldesmon/oxytocin positive, ±CD10).

Leiomyomatous tumours

— malignancy relates to a combination of:
infiltrative margins
cellular atypia
coagulative tumour cell necrosis
mitoses >10/10 hpfs.

Leiomyosarcoma is usually a high-grade lesion with a bulky mass, satellite nodules, areas of necrosis and poor outlook. Variants are typical (spindle cells), epithelioid and myxoid. Cells are smooth muscle actin, desmin, h-caldesmon, oxytocin, calponin and vimentin positive with cross reactivity for cytokeratin (CAM5.2) and variable ER expression.

— uncertain malignant potential:
cellular atypia and mitoses 5–10/10 hpfs indicate probable malignancy if the atypia is moderate or severe.
— cellular leiomyoma:
benign; identify thick-walled vessels and strong desmin positivity to distinguish from an endometrial stromal tumour.
— mitotically active leiomyoma:
benign if no significant cell atypia, abnormal mitoses or coagulative tumour cell necrosis.
— cell type:
myxoid and epithelioid leiomyosarcomas have less cellular atypia and mitotic activity.
— beware pseudomalignancy:
(1) bizarre symplastic leiomyoma. Benign if the symplastic nuclear change is focal, the mitotic count is low (<3/10 hpfs) and coagulative tumour cell necrosis is absent
(2) changes after gonadotrophin analogue treatment, viz. haemorrhage and necrosis, symplastic type nuclear atypia and apparent hypercellularity
(3) intravenous leiomyomatosis with vascular invasion and "metastases" but not malignant.

Choriocarcinoma/placental site trophoblastic tumour (PSTT)
— after abortion, normal or molar pregnancy.
— see Chapter 28.

Lymphoma/leukaemia
— see Chapter 25.

Others
— haemangiopericytoma, angiosarcoma, soft tissue sarcomas and germ cell tumours are all rare.

25
Cervical Carcinoma

1. GROSS DESCRIPTION

Specimen

— cervical smear/punch or wedge biopsy/diathermy (hot) or knife (cold) cone biopsy/LLETZ (large loop excision of transformation zone)/hysterectomy/trachelectomy with laparoscopic lymphadenectomy/radical (Wertheim's) hysterectomy with vaginal cuff, parametria and lymphadenectomy/pelvic (anterior/posterior/ total) exenteration (bladder, ureters, uterus, vagina, tubes and ovaries, rectum)
— size (cm) and weight (g).
— cervical dysplasia and cancer are often detected because of an abnormal smear as part of a cervical screening programme. A persistent or high-grade abnormality is referred for colposcopic visualization of the transformation zone to delineate abnormal areas of mucosa characterized by punctation, mosaicism and loss of uptake of iodine (acetowhite epithelium). Cervical punch biopsy determines the nature of the abnormality which, if localized, is ablated or resected by loop or cone biopsy. Specimens are orientated, serially sliced and all processed with standard step sections to establish the nature (squamous or glandular) and grade of the lesion, the presence of any invasive component and relationship to the exocervical, endocervical and deep margins. Close histocytological correlation is required for accurate reporting and smear follow-up is for 5–10 years with subsequent return to usual screening programme intervals. A significant proportion of established cervical cancers are asymptomatic in the older age group and undiscovered due to non-attendance at cervical smear appointments. Some result from misinterpretation and undercalling of previous smears in what is a screening programme with inevitable false-negative cases. Symptomatic disease (e.g. postcoital bleeding) requires clinical examination and, if a cancer is suspected, a targeted wedge biopsy rather than a punch biopsy taken as this has a greater chance of establishing invasive disease. Tumour staging is by MRI scan (for local spread) and CT scan (for distant spread). Cold cone knife biopsy may be considered for small cancers or if a cervical glandular lesion is suspected but, in general, with tumours greater than stage IA, radical hysterectomy is carried out. In occasional cases a fertility-sparing radical

trachelectomy (cervix, parametria) with laparoscopic lymphadenectomy is performed. Indications for pelvic exenteration are invasion of adjacent organs, recurrent disease and severe pelvic irradiation necrosis. Advanced disease may present with ureteric obstruction and chronic renal failure, haematuria or rectal symptoms.

Tumour

Site
— endocervix/exocervix.
— anterior/posterior.
— lateral (right/left).

Size
— length × width × depth (cm) or maximum dimension (cm).
— stromal invasion: breech of basement membrane with scant stromal penetration <1 mm in depth.
— microinvasion:
depth—≤3 mm (FIGO IA1) or 5 mm (FIGO IA2) depth of invasion from the nearest (surface or glandular) basement membrane, usually involved by CIN/CGIN.
volume—≤500 mm^3 (Burghardt) or ≤5 mm depth ×7 mm horizontal axis (FIGO).
vessels—venous or lymphatic permeation does not alter the staging.

Appearance
— polypoid/papillary/nodular/solid/ulcerated/burrowing. Ulcerated cancers generally infiltrate more deeply than polypoid ones.

Edge
— circumscribed/irregular.

Extent
— infiltration cervical wall, parametria, corpus uteri, vagina.

2. HISTOLOGICAL TYPE

Squamous cell carcinoma
— 80% of cases.
— classical:
keratinizing
non-keratinizing—large cell/small cell. Non-keratinizing large cell is recognizably squamous with intercellular bridges but no keratin pearls are present.

variants:

— verrucous: exophytic and locally invasive. May recur after excision and radiotherapy. Bland cytology with bulbous processes and a pushing deep margin.

— warty: surface koilocytosis and invasive deep margin.
— spindle cell: upper aerodigestive tract analogue with tumour cell fibroplasia (sarcomatoid carcinoma).
— papillary: two types of papillary neoplasm with either CIN-like dysplastic/in-situ squamous, or, squamotransitional type epithelium, the latter in post-menopausal women and associated with late recurrence and metastases (25%). Invasion at the base may be superficial or associated with more usual squamous carcinoma.
— basaloid: aggressive; nests of basaloid cells with peripheral palisading and central keratinization or necrosis.
— lymphoepithelioma-like: circumscribed margin, lymphocytic infiltrate, large uniform cells with prominent nucleolus, and may have better prognosis; radiosensitive. EBV positive.

Adenocarcinoma
— 10–15% of cases.
— endocervical: 70% of cervical adenocarcinomas and variably glandular/mucinous related to the degree of differentiation which is usually well to moderate.
— endometrioid: 25% of cervical adenocarcinomas and exclude uterine carcinoma extending to cervix. Typically at the junctional zone arising from endometriosis/endometrial metaplasia and may coexist with usual endocervical type adenocarcinoma. A minimal deviation variant exists.
— minimal deviation (adenoma malignum): late presentation and poor prognosis with bland epithelium showing mitoses and irregular gland extension deep (>50%) into the cervical stroma. CEA and p53 overexpression may be of diagnostic help. Associated with Peutz-Jeghers syndrome.
— villoglandular: good prognosis in young females. Papillary with CGIN type epithelium, connective tissue cores and indolent invasion at base. More aggressive, moderately differentiated variants occur and it can be associated with more usual cervical cancer subtypes. Also consider implantation from an endometrial primary.
— clear cell: clear, hobnail cells, glycogen PAS positive, solid, tubules, papillae; in utero exposure to diethylstilboestrol (50%).
— serous papillary: poor prognosis and potentially multifocal in endometrium and ovary. High-grade cytological appearances ± psammoma bodies—exclude low-grade villoglandular carcinoma.
— mesonephric: from mesonephric duct remnants deep in the posterior or lateral cervical wall. Small glands with eosinophilic secretions.
— non-Müllerian mucinous: intestinal including colloid and signet ring cell carcinomas. Poor prognosis and exclude gut secondary.

Poorly differentiated carcinoma
— scirrhous, undifferentiated.
— in undifferentiated carcinomas also consider differential diagnoses such as sarcoma (epithelioid leiomyosarcoma), malignant melanoma and malignant lymphoma.

Mixed tumours
— mixed type (e.g. squamous/adenocarcinoma) and differentiation (e.g. endocervical/endometrioid adenocarcinoma).
— adenosquamous, solid with mucus production: varies from well differentiated adenoacanthoma with a good prognosis to poorly differentiated squamous with PAS positive mucin production (up to 30% of cases), which is more aggressive than usual squamous carcinoma.

Miscellaneous carcinoma
— glassy cell: a poorly differentiated adenosquamous carcinoma in young women.
— adenoid basal: indolent and often an incidental finding at hysterectomy or cone biopsy. Organoid lobules and nests of cells with punched-out lumina ± eosinophilic secretions. Strong association (90%) with overlying high-grade CIN or microinvasive squamous cell carcinoma.
— mucoepidermoid and adenoid cystic: low-grade and indolent behaviour although recurrence/metastasis if incompletely removed.

Small cell undifferentiated carcinoma
— primary or secondary. Chromogranin/synaptophysin/CD56 positive with poor prognosis.

Neuroendocrine carcinoma
— atypical carcinoid-like of intermediate-grade malignancy as well as classical carcinoid (rare) and large cell neuroendocrine carcinoma.

Metastatic carcinoma
— direct spread: endometrium (commonest), colorectum, bladder.
— distant spread: breast (especially infiltrating lobular), stomach, ovary.
— tumour may be nodular and stromal with normal overlying surface epithelium.

3. DIFFERENTIATION
Well/moderate/poor/undifferentiated, or Grade 1/2/3/4.
Varies according to lesion type, e.g. keratinizing squamous carcinoma is well to moderately differentiated, non-keratinizing large cell moderate and non-keratinizing small cell poorly differentiated. About 60% are moderately differentiated. Tumour grade does not reliably predict prognosis and is only broadly indicative. However, grade 1 (small amount (≤10%) of solid growth with mild nuclear atypia) has a better prognosis than grade 3 (solid pattern (>50%) with severe nuclear atypia) adenocarcinoma. Undifferentiated carcinomas show no squamous or glandular differentiation (grade 4).

4. EXTENT OF LOCAL TUMOUR SPREAD
Border: pushing/infiltrative.
Lymphocytic reaction: prominent/sparse.
Infiltration:

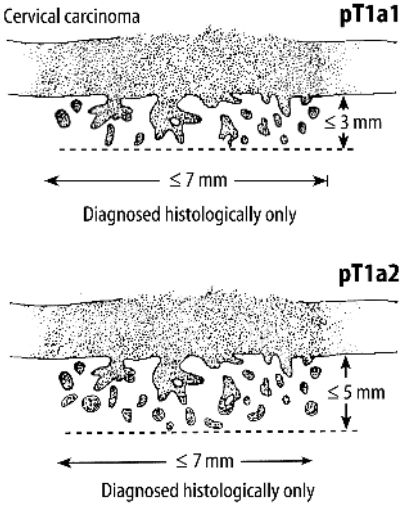


FIGURE 25.1. Cervical carcinoma.

— cervical wall, parametria, endometrium, myometrium, vagina.
— depth through the cervical stroma and parametrium and distance to the nearest parametrial resection margin (mm).

FIGO/TNM

FIGO is based on surgical staging, TNM on clinical and/or pathological classification. The TNM classification applies only to carcinomas.

pTis carcinoma in situ (= CIN III or adenocarcinoma in situ/high-grade CGIN)

pT1 carcinoma confined to the uterus (extension to the corpus is disregarded)
- 1a lesions detected only microscopically; maximum size 5 mm deep and 7 mm across; venous or lymphatic permeation does not alter the staging
- Ia1 ≤3 mm deep, ≤7 mm horizontal axis
- Ia2 3 mm <tumour depth ≤5 mm, ≤7 mm horizontal axis
- Ib clinically apparent lesions confined to the cervix or preclinical lesions larger than stage IA (occult carcinoma)
- Ib1 clinical lesions no greater than 4 cm in size
- Ib2 clinical lesions greater than 4 cm in size

pT2 invasive carcinoma extending beyond the uterus but has not reached either lateral pelvic wall. Involvement of upper two-thirds of vagina, but not lower third
- a. without parametrial invasion
- b. with parametrial invasion

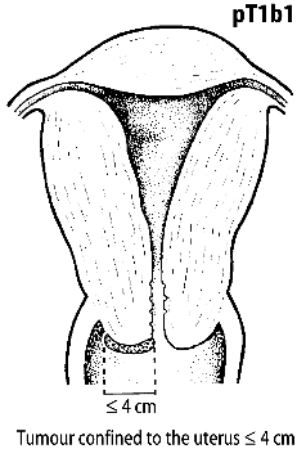


FIGURE 25.2. Cervical carcinoma.

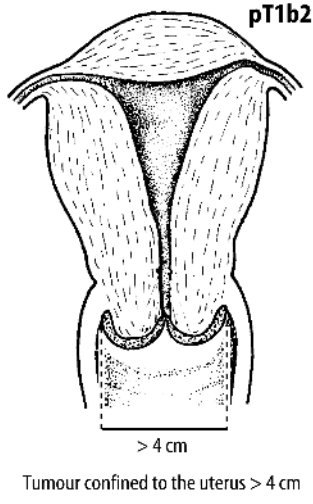


FIGURE 25.3. Cervical carcinoma.

pT3 a. invasive carcinoma extending to either lower third of vagina and/or
b. lateral pelvic wall and/or causes hydronephrosis/non-functioning kidney

pT4 invasive carcinoma involving mucosa of urinary bladder mucosa and/or rectum* or extends beyond the true pelvis.

*Bladder/rectal mucosal involvement requires confirmation by biopsy and involvement of bladder/rectal wall only is pT3a.

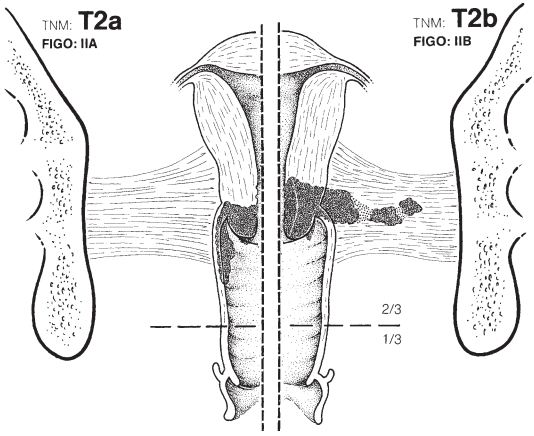


FIGURE 25.4. Cervical carcinoma.

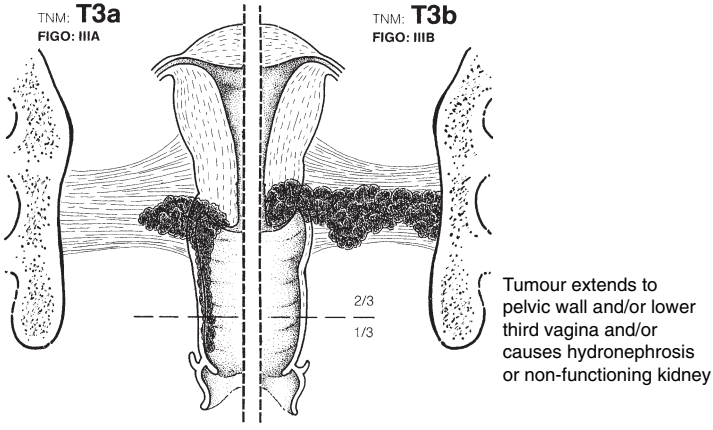


FIGURE 25.5. Cervical carcinoma.

pT2b is used for grossly or histologically evident continuous invasion beyond the myometrium into the parametrium and not for parametrial lymphovascular involvement only. "Frozen pelvis" is a clinical term meaning extension to pelvic wall(s), i.e. pT3b. Positive peritoneal fluid is not considered in the TNM/FIGO classification.

Spread is typically to vagina, uterine corpus, parametria, lower urinary tract (ureters) and uterosacral ligaments. Involvement of regional nodes relates to the stage of disease with lungs, brain and bone the commonest (5–10%) sites of distant metastases.

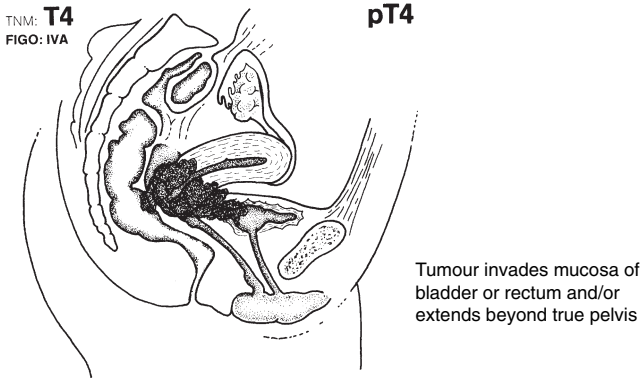


FIGURE 25.6. Cervical carcinoma.

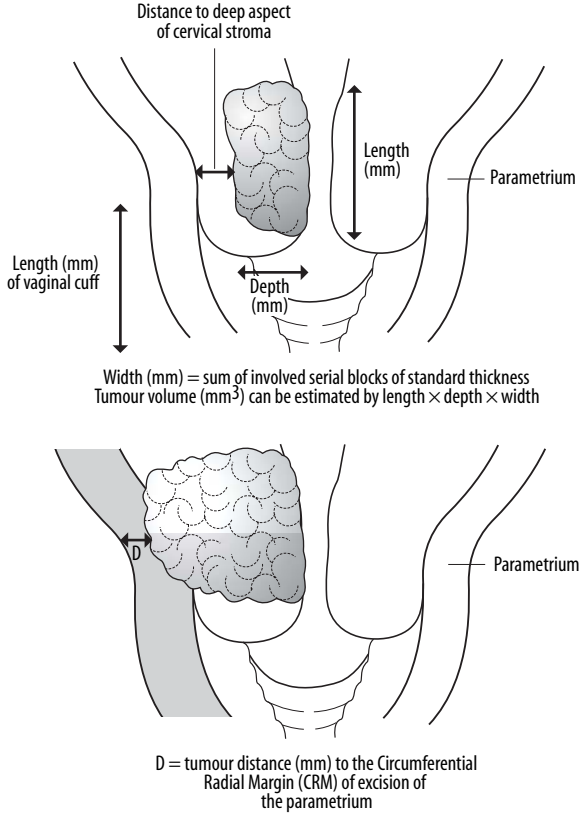


FIGURE 25.7. Cervical carcinoma.

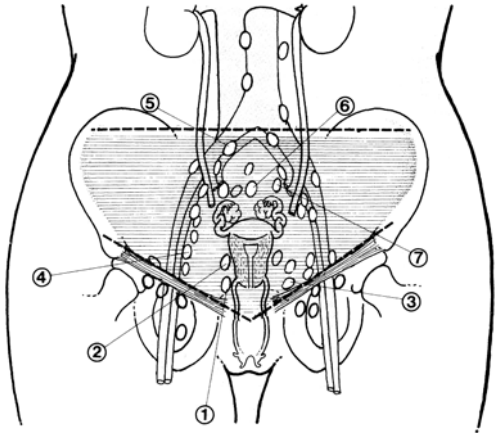


FIGURE 25.8. Cervical carcinoma: regional lymph nodes.

5. LYMPHOVASCULAR INVASION

Present/absent.
Intra-/extratumoral.
Lymphovascular invasion should be noted on biopsy material as it may influence the choice of more extensive surgical resection.

6. LYMPH NODES

Site/number/size/number involved/extracapsular spread.
Parametrial involvement increases regional lymph node metastases to about 35% of cases.
Regional nodes: ① paracervical, ② parametrial, ③ hypogastric (internal iliac, obturator), ⑤ common and ④ external iliac, ⑥ presacral, ⑦ lateral sacral. A regional lymphadectomy will ordinarily include a minimum of 10 lymph nodes. Intraoperative frozen section examination of suspicious lymph nodes may be done as a prequel to radical surgery and, if positive, a more conservative approach adopted.

pN0 no regional lymph node metastasis
pN1 metastasis in regional lymph node(s).

Optional descriptors are:
pN1a—1–2 involved node(s) below the common iliac artery
pN1b—≥3 involved node(s) below the common iliac artery
pN1c—any involved node along the common iliac artery.

7. EXCISION MARGINS

Distances (mm) to the nearest deep cervical (anterior and posterior), lateral parametrial and inferior vaginal resection margins.

In a trachelectomy specimen distances (mm) to the nearest deep cervical, lateral parametrial, proximal endocervical and distal exocervical resection margins.

8. OTHER PATHOLOGY

HPV—human papilloma virus: anogenital field change of viral infection, intraepithelial neoplasia and carcinoma.
CIN—cervical intraepithelial neoplasia.
SIL—squamous intraepithelial lesion (Bethesda system).
AIS/EGD/CGIN—adenocarcinoma in-situ and lesser changes of endocervical glandular dysplasia (cervical glandular intraepithelial neoplasia); low-grade/high-grade EGD/CGIN.
VAIN—vaginal intraepithelial neoplasia
VIN—vulval intraepithelial neoplasia.
AIN—anal intraepithelial neoplasia.
Bowenoid papulosis up—brown perineal patches in young women; HPV induced with histology of VIN III and negligible risk of progression to carcinoma.

Evidence indicates that "high-risk" HPV infection results in high-grade CIN (SIL) with a higher rate of progression to carcinoma. "Low-risk" HPV and low-grade CIN may potentially regress. HPV infection is also an aetiological factor in cervical glandular dysplasia (CGIN), which often coexists with squamous epithelial dysplasia (CIN, SIL).

Low- and high-grade CGIN also potentially progress to microinvasive and invasive disease with a strong association between high-grade CGIN and invasive lesions. CGIN should also be distinguished from benign mimics, e.g. tubo-endometrial metaplasia (TEM), endometriosis, endocervical microglandular hyperplasia, mesonephric remnants and tunnel clusters. CGIN shows an abrupt junction with normal epithelium, nuclear atypia, mitoses and apoptosis. Ciliation is less frequent than in metaplasia. Immunohistochemistry may also be of help in that CGIN has a high (>10%) Ki-67 proliferation index, stains strongly with p16 and p53 and is focal or negative for bcl-2, while benign mimics such as TEM have a converse immunophenotype with this panel. Interobserver variation is good for high-grade CGIN but poor for low-grade. Endocervical (commonest), intestinal and endometrioid variants are described. Ki-67 positive cells in the upper two-thirds of the epithelium also reliably identifies CIN lesions.

"low-risk"	HPV types 6, 11	condylomas, CIN I
"high-risk"	HPV types 16, 18, 31, 33, 35, 39, 51	CIN II/III squamous carcinoma
	typing by in-situ hybridization	
CIN (SIL)	low-grade	CIN I, SIL I
	high-grade	CIN II, CIN III, SIL II

"High-risk" HPV DNA subtyping may have a role to play in the closer follow-up of women whose cervical smears show BNA (borderline nuclear abnormalities)/ASC-US (atypical squamous cells of uncertain significance) changes and low-grade CIN/SIL.

Cervical squamous cell carcinoma and adenocarcinoma are cytokeratin and CEA positive.

Microinvasion

The higher the grade and larger the CIN lesion the more likely it is to show microinvasion with a 35% chance of CIN III progressing to carcinoma over a 10-year period. Microinvasive carcinoma is not designated on small, limited biopsy samples but rather on a large biopsy specimen, e.g. cone biopsy, which allows removal and assessment of the whole lesion. Five-year survival rates are about 95%. Risk factors for progression to frankly invasive carcinoma are increasing depth of invasion, increasing lateral extent (horizontal axis) of the lesion, lymphovascular invasion and incomplete removal by LLETZ/cone biopsy. Adverse factors in occult carcinoma (i.e. bigger than microinvasion but not clinically detectable) are a depth >5 mm and lymphovascular invasion. Very occasional cases, where the CIN lesion has focal areas suspicious of penetrating the stroma but lacking definite evidence of invasion, warrant a designation of "questionable stromal invasion". Commonly occurring tangential cutting and extension of CIN into endocervical crypts must be excluded and is supported by an intact circumscribed basement membrane. An uncommon differential is squamous carcinoma with a CIN III-like growth pattern and widespread, deep expansion with luminal necrosis are useful diagnostic clues.

The first stage of microinvasive squamous cell carcinoma is recognized by budding of invasive cells with morphology similar to that of the overlying CIN lesion through the basement membrane. With lesion progression the tongues of tumour become more differentiated with cytoplasmic eosinophilia and nuclear clearing. A stromal fibro-inflammatory reaction is also seen. The distinction between adenocarcinoma in situ and early invasive adenocarcinoma is more difficult to define and measure with features such as depth, complexity and budding of glandular architecture and stromal reaction of use. Measurement of tumour extent in cervical carcinoma is readily obtained in the longitudinal and deep axes, whereas the transverse dimension depends on summation of the number of involved adjacent blocks of known thickness. Microinvasive carcinoma may be treated with loop or cold knife cone biopsy ensuring a minimum 3-mm clearance of margins (note that there can be a small risk of skip or higher endocervical canal lesions) or simple hysterectomy. A fertility-sparing procedure such as radical trachelectomy (removal of the cervix and surrounding parametria with laparoscopic lymphadenectomy) may be considered in young women with up to a 1b1 tumour <2 cm in maximum dimension. Radial hysterectomy is indicated for larger tumours or where there is lymphovascular invasion. Radiotherapy produces tumour cell necrosis, degeneration, pleomorphism, maturation, inflammation and fibrosis. Combination radio-/chemotherapy is used to augment radical surgery or on its own for palliative control in high-stage disease.

Prognosis

Prognosis relates to tumour type and volume, invasion of endometrium, parametrium and vessels and, most importantly, stage of disease. Overall

5-year survival rate is 55%, with stage I carcinoma 85–90% and 35%/10% for stage III/IV. Tumours with a glandular component, lymphovascular invasion and young age at diagnosis (<30 years) are more aggressive and more often positive for pelvic node metastases. The incidence of cervical adenocarcinoma is increasing and presents on average 5 years younger than squamous carcinoma. Since it has a worse prognosis than equivalent squamous cell tumours, more radical surgery is undertaken. Mixed differentiation tumours, and the coexistence of CIN and CGIN particularly on the surface and in crypts, respectively, are not uncommon. High-grade CGIN or adenocarcinoma in situ is usually treated by hysterectomy, although conservative conization may be used if the patient is young (<36 years) and wishes to remain fertile.

9. OTHER MALIGNANCY

Malignant melanoma
— usually metastatic.
— primary lesion rare: 40% 5-year survival.

Embryonal rhabdomyosarcoma
— infancy/childhood.
— syn. sarcoma botryoides.
— cellular subepithelial cambium zone/myxoid zone/deep cellular zone.
— small cells/rhabdomyoblasts/desmin, myogenin and myo D1 positive.
— ± heterologous elements.

Leiomyosarcoma
— 40–60 years.
— cellular atypia/ necrosis/>5 mitoses/10 hpfs.
— >10 mitoses/10 hpfs if no atypia.

Adenosarcoma
— polypoid.
— 25% have heterologous elements (striated muscle, cartilage, fat).
— low-grade malignancy.

Stromal sarcoma and malignant mixed mesodermal tumour are more likely to represent spread to the cervix from an endometrial lesion rather than a primary tumour.

Lymphoma
— more often secondary spread from systemic/nodal disease.
— primary: 70% are intermediate to high-grade of large B-cell type.
— 5-year survival about 75%.

Leukaemia
— granulocytic sarcoma as a presentation of chronic myeloid leukaemia.
— CD68/chloroacetate esterase /myeloperoxidase positive.
— relapse of AML (acute myeloid leukaemia), blast transformation of CML.

26
Vaginal Carcinoma

1. GROSS DESCRIPTION

Specimen

— vaginal smear/biopsy/partial/subtotal vaginectomy/radical vaginectomy (with hysterectomy, salpingo-oophorectomy and lymphadenectomy)/pelvic exenteration.
— weight (g) and size (cm), number of fragments.
— vaginal pathology may be asymptomatic or present with bleeding, discharge, dyspareunia, a feeling of discomfort or mass. Clinical examination and direct visualization by colposcopy can show dysplastic mucosal lesions (VAIN), warts, tumour and even changes related to diethylstilboestrol (DES) exposure (see below). Vaginal smear, punch or wedge biopsy allow a tissue diagnosis and the strong association with previous vulval, cervical and endometrial disease must be taken into account. Pelvic MRI is used to stage suspected tumour including the presence of any pelvic or inguinal lymphadenopathy, with the latter sometimes also amenable to investigation by FNA cytology. Surgery in the form of radical vaginectomy is used for localized, non-responsive or recurrent tumours, otherwise chemoradiation subject to assessment and discussion at a multidisciplinary meeting. Laser ablation and topical 5-fluorouracil are additional options for superficial mucosal wart or VAIN lesions. Pelvic exenteration is sometimes used for extensive local disease or post radiotherapy necrosis.

Tumour

Site

— anterior/posterior/lateral (right or left). Usually anterior or lateral and upper third (50–60%).

Size

— length × width × depth (cm) or maximum dimension (cm).

Appearance

— polypoid/verrucous/papillary/sessile/ulcerated/pigmented.
— exophytic lesions are commoner than endophytic and most are either nodular or ulcerative.

Edge
— circumscribed/irregular.

2. HISTOLOGICAL TYPE

Squamous cell carcinoma
— 90–95% of primary vaginal carcinomas.
— keratinizing/non-keratinizing.
— large cell/small cell.
— mainly moderately differentiated keratinizing.

variants:

— verrucous: exophytic, bland cytology with deep bulbous processes and a locally invasive pushing margin.
— warty (condylomatous): with focal invasion at the base.
— spindle cell: a cytokeratin positive sarcomatoid carcinoma.

Adenocarcinoma
— clear cell: PAS positive for glycogen, solid/tubules/papillae. From 1970 to 2000 most patients were 14–25 years with in utero exposure to DES. Following withdrawal of DES and as this cohort ages this diagnosis is decreasing. Non-DES cases in the older age group are rare, comprising clear/hobnail cells ± vaginal adenosis defined as the presence of any Müllerian type glandular epithelium, often endocervical, or tuboendometrial in character. Differential diagnosis is vaginal adenosis with microglandular hyperplasia and Arias-Stella reaction in pregnancy or hormone therapy. Prognosis is relatively good (80% 5-year survival) if small and superficial. Otherwise local recurrence and nodal metastases usually within 3 years but sometimes late after many years.
— endometrioid: possibly arising from previous endometriosis.
— mucinous: endocervical or intestinal in type and the former may be associated with adenosis (endocervicosis). Note that rarely primary vaginal intestinal-type adenoma of tubular/villous morphology can occur.
— mesonephric: deep in lateral vaginal walls arising from mesonephric remnants.

Adenosquamous carcinoma
— mixed differentiation of worse prognosis.

Adenoid cystic carcinoma
— indolent with late local recurrence and potential for metastases.

Adenoid basal carcinoma
— indolent.

Small cell carcinoma
— primary or secondary from cervix or lung.

Undifferentiated carcinoma
— no squamous or glandular differentiation.

Transitional cell carcinoma
— primary (rare) or in association with concurrent bladder/urethral carcinoma.

Carcinoid tumour
— chromogranin/synaptophysin/CD56 positive.

Endodermal sinus tumour
— yolk sac spectrum of appearances and AFP positive in posterior wall and fornices of infants. Responsive to surgery and chemotherapy.

Malignant melanoma
— 3% and mucosal junctional activity indicates a primary lesion. Poor prognosis.
— more often represents a metastasis, e.g. from urethra or vulva.

Metastatic carcinoma
— comprises 80% of malignant vaginal tumours, far outnumbering primary lesions.
— direct spread: cervix, endometrium, rectum, vulva, bladder, urethra.
— distant spread: kidney, breast, gut, ovary.

The commonest metastases (cervix, endometrium, gut) are usually in the upper third of the vagina and may be submucosal. Other metastatic tumour types should also be considered, e.g. vaginal recurrence of vulval or urethral malignant melanoma, or uterine leiomyosarcoma.

3. DIFFERENTIATION/GRADE
Well/moderate/poor/undifferentiated, or Grade 1/2/3/4.

There is no specific recommended grading system for vaginal tumours with squamous or glandular differentiation other than the above. Grade 4 (undifferentiated) tumours show no differentiation. Transitional cell carcinomas are designated WHOI/II/III based on cytonuclear grade.

4. EXTENT OF LOCAL TUMOUR SPREAD
Border: pushing/infiltrative.
Lymphocytic reaction: prominent/sparse.

FIGO/TNM
FIGO is based on clinical staging, TNM on clinical and/or pathological classification. It applies to primary carcinoma of the vagina only excluding secondary growths either by metastasis or direct extension, e.g. from cervix or vulva.

Category of microinvasive carcinoma is not established, although superficial tumours invading ≤3 mm with no lymphovascular invasion have a low incidence of nodal metastases.

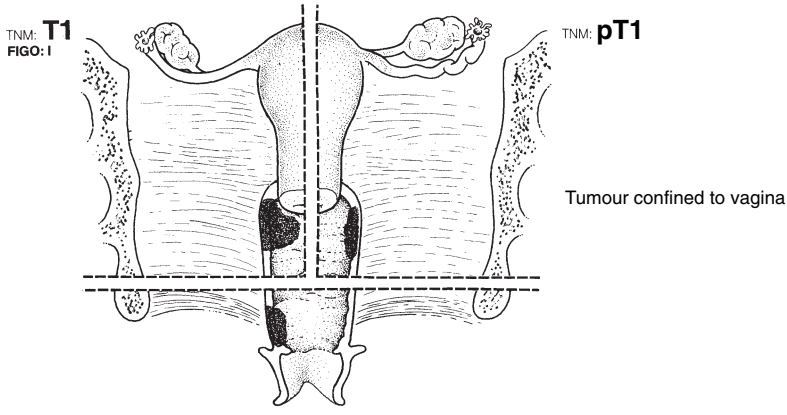


FIGURE 26.1. Vaginal carcinoma.

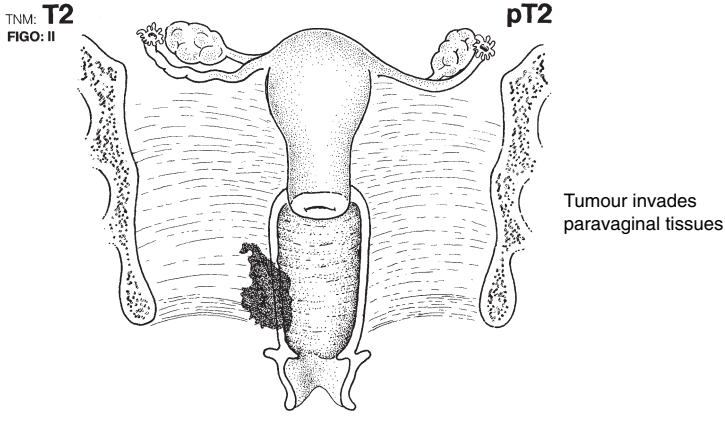


FIGURE 26.2. Vaginal carcinoma.

pTis	carcinoma in situ
pT1	tumour confined to the vagina
pT2	tumour invades paravaginal tissues but does not extend to pelvic wall
pT3	tumour extends to pelvic wall*
pT4	tumour invades mucosa of bladder or rectum, and/or extends beyond the true pelvis.

*The pelvic wall is defined as muscle, fascia, neurovascular structures or skeletal elements of the bony pelvis.

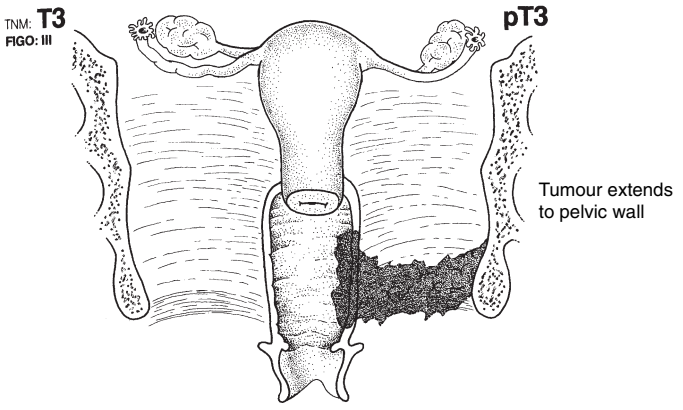


FIGURE 26.3. Vaginal carcinoma.

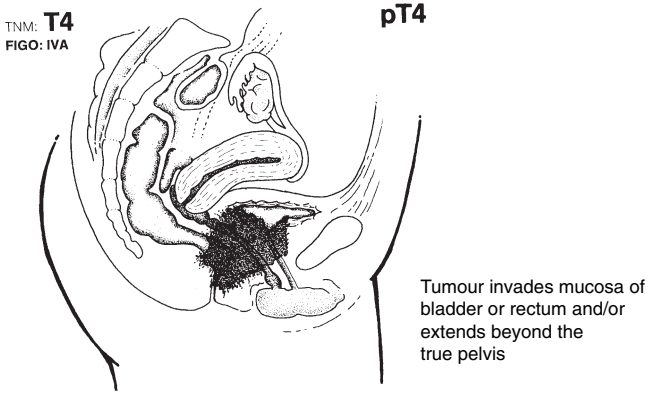


FIGURE 26.4. Vaginal carcinoma.

Invasion of the rectal or bladder wall is pT2, while mucosal involvement is pT4. "Frozen pelvis" is a clinical term meaning tumour extension to the pelvic wall(s) and is classified as pT3.

Spread is mainly by early direct invasion and lymph node metastases, with 50% beyond the vagina (pT2) at presentation and 25% in the rectum or bladder (pT4).

M1 disease is either an upper two-thirds vaginal tumour with inguinal node metastases, or a lower third vaginal tumour with pelvic node metastases. Other distant sites include lung, liver and brain.

5. LYMPHOVASCULAR INVASION
Present/absent.
Intra-/extratumoral.

6. LYMPH NODES
Site/number/size/number involved/extracapsular spread.
Regional nodes: upper two-thirds—obturator, internal iliac, external iliac, pelvic nodes; lower third—inguinal and femoral nodes.
A regional lymphadenectomy will ordinarily include a minimum of six (inguinal) or 10 (pelvic) lymph nodes.

pN0 no regional lymph node metastasis
pN1 metastasis in regional lymph node(s).

7. EXCISION MARGINS
Distances (mm) to the nearest longitudinal resection limit and deep circumferential radial margin. The presence of epithelial (squamous or glandular) dysplasia or atypical adenosis at a mucosal resection margin may increase the frequency of recurrent tumour.

8. OTHER PATHOLOGY

Vaginal intraepithelial neoplasia (VAIN): grades I/II/III
— rarer and less well established than the CIN or VIN/cancer sequences.

Cervical intraepithelial neoplasia (CIN)/Anal intraepithelial neoplasia (AIN)
HPV 16/18 is a common aetiology in CIN, VAIN, AIN and VIN (vulva) and is instrumental in the field change effect of carcinogenesis in the female genital tract, which results in synchronous or metachronous cancers in the vulva, cervix and vagina. The vagina is also a common site of direct spread from vulva and cervix carcinomas and it should be noted that the commonest vaginal malignancies are secondary cervical and endometrial carcinoma. Knowledge of a relevant history and availability of slides for comparison are, therefore, crucially important in designation of any vaginal lesion. A not uncommon differential for adenocarcinoma on vaginal smear or vault biopsy is post-hysterectomy prolapsed fallopian tube or endometriosis.

Prognosis
Initial treatment of vaginal carcinoma is by irradiation, with better response for squamous cell carcinoma than for adenocarcinoma, malignant melanoma and sarcoma. Surgery is used for early stage disease, non-responsive cases or local recurrence. Upper vaginal lesions tend to recur locally while lower vaginal tumours are prone to developing distal or pelvic side wall disease.

Prognosis relates strongly to disease stage, e.g. 43% 5-year survival with 70% for stage I and 30% for stage III. Vaginal malignant melanoma

spreads early to pelvic soft tissues, lymph nodes, peritoneum, lung and bone with 5-year survival rates of 21%.

9. OTHER MALIGNANCY

Lymphoma/leukaemia
— lymphoma is usually secondary to systemic disease. Rare primary lesions are intermediate to high-grade large B cell in type.

Embryonal rhabdomyosarcoma (sarcoma botryoides)
— infants/children <5 years of age, anterior vaginal wall.
— superficial subepithelial cambium layer, intermediate myxoid zone, deep cellular zone, desmin/myo D1/myogenin positive.
— locally aggressive necessitating primary chemotherapy ± surgery and irradiation.

Leiomyosarcoma
— usually >3 cm, with cell atypia and ≥5 mitoses/10 hpfs.
— a primary lesion is rare: consider metastases, e.g. uterine leiomyosarcoma.

Müllerian stromal sarcomas and other sarcomas
e.g. alveolar soft part, malignant fibrous histiocytoma, synovial sarcoma.

27
Vulval Carcinoma

1. GROSS DESCRIPTION

Specimen

— biopsy/partial/simple/radical vulvectomy/uni-/bilateral inguinal lymphadenectomy/pelvic exenteration.
— size (cm) and weight (g).
— vulval cancer forms 5% of gynaecological malignancies and occurs mainly in women aged 60–75 years. It can present as itch in an area of pallor or redness (leukoplakia/VIN) on a background of atrophic or hypertrophic lichen sclerosus. A nodular, verruciform or ulcerating mass may be present and a diagnostic wedge or punch biopsy taken with the former more likely to establish the presence of any invasive disease and the latter sufficient for abnormalities in a flat epithelium such as VIN. CT and MRI scan can be used to detect and stage inguinal lymphadenopathy, which may also be amenable to FNA cytology. Because of the strong HPV association, concurrent cervicovaginal disease is excluded. Surgical treatment is geared to the patient's age, fitness, tumour site and stage with wide local excision for "early" stage IA disease. Central and lateral stage IB lesions may be treated by partial vulvectomy and bilateral or ipsilateral groin node dissection, respectively. Stage II cancers and above need radical vulvectomy, which includes removal of the perianal skin and bilateral inguinal lymphadenectomy. Pre-operative radiotherapy may be given for tumours with extensive local invasion or involved nodes in an attempt to downstage, facilitate surgery and avoid pelvic exenteration.

Tumour

Site

— anterior/posterior.
— lateral (right/left).
— labia majora/labia minora/clitoris.
— labia majora is the commonest site, then labia minora and clitoris.
— bilateral (25%).

Size

— length × width × depth (cm) or maximum dimension (cm).

Appearance
— polypoid/verrucous/ulcerated/necrotic/satellite lesions/pigmented.
— 50% are ulcerated, 30% exophytic.

Edge
— circumscribed/irregular.

2. HISTOLOGICAL TYPE
Vulval carcinomas show the full range of cutaneous cancers.

Squamous cell carcinoma
— 80–90% of malignant vulval neoplasms.
— keratinizing or non-keratinizing and of two main types.
a. 60% of cases are in older women, not related to HPV and a keratinizing squamous cell carcinoma with adjacent epidermal hyperplasia/hyperkeratosis/differentiated VIN, or,
b. 30% of cases are in younger women, HPV 16/18 positive, of basaloid or warty histology and with adjacent VIN of undifferentiated or classic type (see 8. Other pathology for discussion).

variants:

— basaloid: 28% of cases at a younger age (<60 years) and association with HPV, cervical and vaginal lesions. Nests of basaloid cells with peripheral palisading, central focal keratinization and mitoses.
— warty: association with HPV and koilocytosis. Prognosis intermediate between usual squamous carcinoma and verrucous carcinoma. Distinguish from pseudoepitheliomatous hyperplasia overlying lichen sclerosus, Crohn's disease or granular cell tumour.
— adenoid: pseudoglandular/acantholytic.
— verrucous: exophytic with pushing deep margin of cytologically bland bulbous processes. Local recurrence after incomplete excision or radiotherapy.
— spindle cell: cytokeratin positive sarcomatoid carcinoma.

Basal cell carcinoma
— 20% local recurrence rate and metastases are rare.

Distinguish from basaloid squamous carcinoma, Merkel cell tumour and secondary small cell carcinoma.

Adenocarcinoma
— rare.
— appendage origin/Bartholin's gland/mesonephric duct remnants, or metastatic.

Paget's disease
— 2% of vulval malignancy.
— intraepithelial adenocarcinoma cells probably arising from basal layer multipotential cells differentiating along sweat gland lines. In

10–20% there is a locoregional or extragenital malignancy, e.g. vulval appendage tumour or bladder carcinoma, cervical or endometrial carcinoma, anorectal carcinoma, breast carcinoma. Immunohistochemistry may help to indicate a possible bladder (uroplakin III/CK7/20 positive) or anorectal (CK20 positive) origin. GCDFP-15 can be positive in vulval Paget's disease and metastatic breast cancer.
— multifocal: check margins histologically as there is a 40% recurrence rate. Mucin stains and immunohistochemistry (EMA, CEA, CAM5.2, cytokeratin 7 positive) may be necessary to distinguish from Bowenoid VIN (AE1/AE3 positive, CAM5.2/CEA/CK7 negative) and superficial spreading malignant melanoma (S100, HMB-45, melan-A positive).

Paget's disease without an associated neoplasm has a very good prognosis but it may also, per se, progress to invasive carcinoma and nodal metastases if beyond the microinvasive stage.

Merkel cell carcinoma
— exclude secondary small cell carcinoma from lung.
— aggressive neuroendocrine carcinoma.
— CAM5.2 (paranuclear dot), cytokeratin 20, chromogranin/synapophysin/CD56 positive. Lung small cell carcinoma is cytokeratin 20 negative/TTF-1 positive.

Malignant melanoma
— 3–10% of malignant vulval neoplasms.
— usually mucosal and cutaneous involvement with Breslow depth and clinical stage the main prognostic indicators.

Metastatic carcinoma
— 5% of malignant vulval neoplasms.
— direct spread: cervix (50% of cases), endometrium, vagina, urethra, bladder, anorectum.
— distant spread: ovary, kidney, breast, lung, malignant melanoma, choriocarcinoma.

Secondary urethral tumours are squamous cell carcinoma, transitional cell carcinoma or malignant melanoma.

3. DIFFERENTIATION
Well/moderate/poor/undifferentiated, or Grade 1/2/3/4.

— well >50%; moderate 20–40% of cases.
— there is no specific recommended grading system for vulval tumours other than the above which should broadly reflect that of non-melanocytic cutaneous carcinomas. Grade 4 (undifferentiated) tumours show no squamous or glandular differentiation.

4. EXTENT OF LOCAL TUMOUR SPREAD
Border: pushing/infiltrative. An irregular infiltrative margin has a higher incidence of nodal metastases.

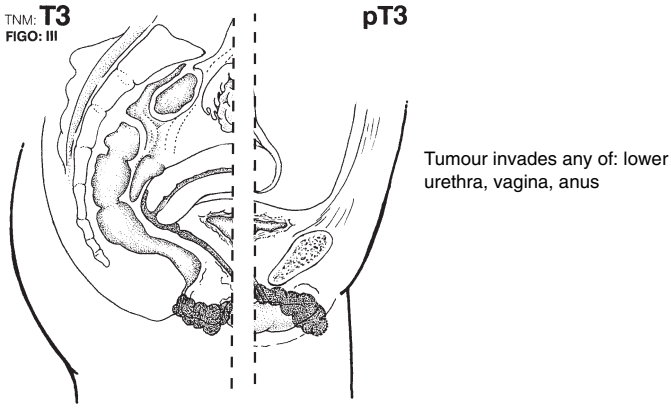


FIGURE 27.1. Vulval carcinoma.

Lymphocytic reaction: prominent/sparse.

Microinvasion ≤3 mm: use of this nomenclature should be avoided as some of these carcinomas will have nodal metastases and invasive lesions >1 mm in depth should probably have radical surgery. Superficially invasive squamous cell carcinoma is defined as a single lesion measuring ≤2 cm diameter and with a depth of invasion ≤1 mm, i.e. pT1a.

Distance (mm) to the nearest painted surgical margin (lateral cutaneous, medial mucosal, deep subcutaneous).

Involvement of vagina, urethra, perineum, anus.

FIGO is based on surgical staging, TNM on clinical and/or pathological classification. The TNM classification applies to primary carcinomas of the vulva only.

pTis	carcinoma in situ
pT1	tumour confined to vulva/perineum ≤2 cm in greatest dimension
	a. stromal invasion ≤1 mm*
	b. stromal invasion >1 mm
pT2	tumour confined to vulva/perineum >2 cm in greatest dimension
pT3	tumour of any size and invades any of: lower urethra/vagina/anus
pT4	tumour invades any of: bladder mucosa/rectal mucosa/upper urethra or is fixed to pubic bone.

Invasion of bladder or rectal wall is pT3 and mucosal involvement pT4. Upper urethra (pT4) is proximal, lower urethra (pT3) is distal. Invasion of urethral wall (only) is pT3.

Spread is direct to the vagina, urethra, anus, inferior pubic and ischial rami and ischiorectal fossae.

*From the epithelial–stromal junction of the adjacent most superficial dermal papilla. Thickness is from the surface, or if there is keratinization, from the deep aspect of the granular layer to the deepest point of invasion.

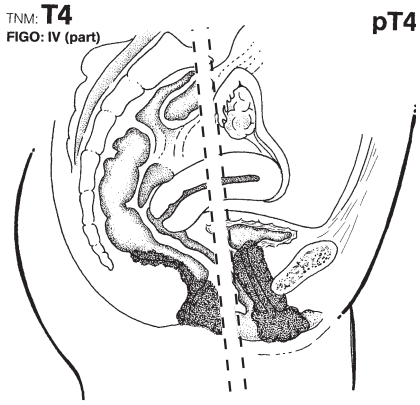


FIGURE 27.2. Vulval carcinoma.

5. LYMPHOVASCULAR INVASION

Present/absent.
Intra-/extratumoral.
Carcinomas invading > 1 mm have a higher incidence of lymphovascular invasion and lymph node metastases and the vulval subepithelial connective tissues have a particularly rich vascular network.

6. LYMPH NODES

Site/number/size/number involved/extracapsular spread.
Regional nodes: femoral and inguinal. A regional lymphadenectomy will ordinarily include a minimum of six lymph nodes.

pN0 no regional lymph node metastasis
pN1 unilateral regional lymph node metastasis
pN2 bilateral regional lymph node metastasis.

Labial tumours go initially to inguinal nodes whereas clitoral lesions may go directly to deep nodes. Ulcerated tumours can produce reactive regional lymphadenopathy mimicking metastatic disease and this can be further investigated by FNA cytology.

7. EXCISION MARGINS

Distances (mm) of tumour and VIN to the nearest painted cutaneous and subcutaneous excision margins and anal, vaginal, urethral limits.

8. OTHER PATHOLOGY

Lichen sclerosus

— atrophic, or hyperplastic with hyperkeratosis (mixed dystrophy).
— associated with (5–25% of cases) but low risk (5%) of progression to carcinoma.
— overexpresses p53 and sometimes shows basal layer atypia.

Condyloma
— warty (condyloma accuminatum) or flat and caused by HPV 6/11 with koilocytosis.

Bowenoid papulosis
— brown perineal patches in young women.
— HPV induced.
— histology of VIN III.
— negligible risk of progression to carcinoma.

Vulval intraepithelial neoplasia (VIN) grades I/II/III
— typically multifocal and present in the adjacent epithelium of 60–70% of cases of squamous carcinoma.
— progression to carcinoma is in the order of 10–20%.
— classic, or, variant types.

Classic or undifferentiated: includes Bowenoid/warty type (young, HPV, associated cervical and anal disease) and basaloid type (old, de novo, resembles CIN III).

Variant: simplex or differentiated VIN with maturation, hyperplasia, hyperkeratosis, variable parabasal atypia and overexpression of p53.

Prognosis

Nearly 30% of vulval squamous carcinomas have metastasized to inguinal or pelvic nodes at presentation. Prognosis relates to tumour size, an infiltrative tumour margin, depth of invasion, vascular involvement and, in particular, nodal disease. Stage I lesions have a 5-year survival of 85%, stage II 60%, stage III 40%, stage IV 20% and overall 50–75%. Treatment is by vulvectomy with uni-/bilateral inguinal lymph node dissection. A limited local excision with wide (1 cm) surgical margins may be used in early-stage (well-differentiated superficially invasive) disease or medically unfit patients. VIN III may be treated by topical therapy, laser, electrocoagulation, wide local excision, partial/total or skinning vulvectomy. Pelvic exenteration is reserved for locally extensive disease. Prognosis of malignant melanoma relates to tumour thickness and depth of invasion at the time of presentation, with average 5-year survival of 30–35%.

9. OTHER MALIGNANCY

Lymphoma/leukaemia
— secondary to systemic disease usually diffuse large B cell in type.

Adnexal/Bartholin's gland carcinomas
— rare and arising from eccrine or apocrine glands, when distinction from metastatic ductal carcinoma of the breast can be problematic.

Bartholin's gland carcinoma forms 1–5% of vulval neoplasms and shows a range of differentiation: squamous cell, adenocarcinoma, mixed

adenoid cystic/mucoepidermoid carcinoma. Ideally an origin from adjacent Bartholin's gland structures should be demonstrable. Five-year survival rates vary from 40% to 80% depending on the stage at presentation.

Aggressive angiomyxoma

— myxoid stroma, prominent vessels and spindle cells. A locally infiltrative vulvovaginal tumour in young women, the edges of which are difficult to define surgically and therefore problematic to resect with ischiorectal and retroperitoneal recurrence a likelihood. Vimentin, actin positive ± desmin. They are also ER and progesterone receptor positive, raising a possible role for hormonal therapy.

Sarcomas

— leiomyo-/rhabdo-/liposarcoma.
— leiomyosarcoma: >5 cm diameter, infiltrating margins, >5–10 mitoses/10 hpfs, cellular atypia.
— rhabdomyosarcoma occurs in childhood and young adults with vaginal disease being embryonal in type and vulval alveolar; desmin/myo D1/myogenin positive.
— liposarcoma: well-differentiated adipocytic/atypical lipoma in type.

Others

— dermatofibrosarcoma protuberans, epithelioid sarcoma, malignant rhabdoid tumour.

28
Gestational Trophoblastic Tumours

1. GROSS DESCRIPTION

Specimen

— curetting/hysterectomy.
— weight (g) and size (cm), number of fragments, villous diameter.
— molar pregnancy usually presents with first trimester bleeding, a uterus larger than expected for gestational dates, absence of fetal parts on ultrasound examination and markedly elevated serum βHCG. Partial moles present with spontaneous abortion and trophoblastic disease should be considered when there is continued vaginal bleeding following delivery or an abortion.

Tumour

Site

— endometrial/myometrial/extrauterine: serosa
parametria
adnexae.
— fundus, corpus, isthmus—cavity.

Size

— length × width × depth (cm) or maximum dimension (cm). Size >5 cm is prognostically adverse.

Appearance

— haemorrhagic/necrotic/vesicular/nodular/polypoid masses.

Edge

— circumscribed/irregular.

2. HISTOLOGICAL TYPE

Choriocarcinoma

— suspect on curettings if: abundant necrotic/ haemorrhagic decidua, bilaminar aggregates of exuberant syncytiotrophoblast and cytotrophoblast and *no* chorionic villi.

— 50% are preceded by a molar gestation: also seen after normal pregnancy (20%) or spontaneous abortion (30%).
— 2–3% of complete moles progress to choriocarcinoma.
— destructive myometrial and vascular invasion are common, leading to haematogenous spread to lung (60–80%), vagina (30%), pelvis (20%) and liver (17%).
— HCG/cytokeratin/inhibin positive/HPL (human placental lactogen) focal.
— 5-year survival >90% with chemotherapy (uterine disease >95%, metastatic disease 83%).

Invasive hydatidiform mole (chorioadenoma destruens)
— 16% of complete moles.
— penetration into the myometrium or uterine vasculature ± adjacent structures of molar villi associated with variable degrees of trophoblast hyperplasia. Haemorrhage and perforation can occur.
— haematogenous transport of "metastatic" nodules to vagina, lung and CNS. They do not affect the prognosis but may present with per vaginum bleeding or haemoptysis and respond well to chemotherapy.

Placental site trophoblastic tumour (PSTT)
— mostly following a normal term pregnancy (75%).
— polypoid mass composed of monomorphic intermediate trophoblast–mononuclear cytotrophoblast ± multinucleated cells, dissecting myofibres without necrosis or haemorrhage. Peri-/intravascular growth patterns.
— HCG negative, HPL/alpha-inhibin/cytokeratin positive.
— 10–15% malignant (mitoses >2/10 hpfs, deep invasion, clear cells): not chemoresponsive and requires surgical removal.

Epithelioid trophoblastic tumour (ETT)
— along with choriocarcinoma and PSTT a non-villous forming potentially malignant gestational trophoblastic tumour.
— very rare, following normal pregnancy.
— geographical areas of necrosis with islands of uninucleate polygonal eosinophilic cells.
— cytokeratin/alpha-inhibin positive: mostly HCG/HPL negative.
— behaviour similar to PSST rather than choriocarcinoma.

Differential diagnosis for choriocarcinoma, PSTT and ETT include persistent molar tissue, undifferentiated carcinoma and epithelioid leiomyosarcoma.

3. DIFFERENTIATION
See above.

4. EXTENT OF LOCAL TUMOUR SPREAD
Border: pushing/infiltrative
Lymphocytic reaction: prominent/sparse. Improved prognosis with an intense tumour–stroma interface inflammatory infiltrate in choriocarcinoma.

The TNM classification applies to choriocarcinoma, invasive hydatidiform mole and placental site trophoblastic tumour. Histological confirmation is not required if the HCG level is abnormally elevated.

TNM (FIGO)

pT1 (I)	tumour confined to the uterus
pT2 (II)	tumour extends to other genital structures: vagina, ovary, broad ligament, fallopian tube by metastasis or direct extension
pM1a (III)	metastasis to the lung(s)
pM1b (IV)	other distant metastasis with or without lung involvement (brain, liver, kidney, gut).

FIGO stages I–IV are subdivided into A (low risk) and B (high risk) categories according to a multiparameter prognostic score (Table 28.1). A more recent modification of FIGO is to qualify the stage with the prognostic score, e.g. III: 4 instead of III A.

5. LYMPHOVASCULAR INVASION

Present/absent.

Intra-/extratumoral.

Physiological trophoblast in placental site reaction is frequently endovascular with potential for myometrial invasion and this must not be over interpreted as malignancy.

Molar tissue can potentially spread to cervix, vaginal wall and vulva through a much dilated pelvic vasculature.

Choriocarcinoma typically shows *destructive* myometrial and vascular invasion.

6. LYMPH NODES

Usually tertiary metastases from a large extrauterine lesion and of poor prognosis. Classified as metastatic MIb disease.

Table 28.1 Prognostic score for gestational trophoblastic tumours

Prognostic score	0	1	2	3
Prognostic factor				
Age	<40	≥40		
Antecedent pregnancy	H. mole	Abortion	Term pregnancy	
Months from index pregnancy	<4	4 to <7	7–12	>12
Pretreatment serum hCG (IU/ml)	$<10^3$	10^3 to $<10^4$	10^4 to $<10^5$	$\geq 10^5$
Largest tumour size including uterus	<3 cm	3 to <5 cm	≥5 cm	
Sites of metastasis	Lung	Spleen, kidney	Gastrointestinal tract	Liver, brain
Number of metastasis		1–4	5–8	>8
Previous failed chemotherapy			Single drug	2 or more drugs

Risk categories: total prognostic score 7 or less is low risk (add "A" to FIGO Stage); total prognostic score 8 or more is high risk (add "B" to FIGO Stage).

7. EXCISION MARGINS

Distances (mm) to the serosa and parametrial resection limits.

8. OTHER PATHOLOGY

Complete hydatidiform mole

— androgenetic diploid 46XX.
— diffuse villous vesicular swelling, although this is only well developed beyond 12 weeks.
— central cistern formation.
— circumferential/multifocal trophoblast; grading the degree of trophoblast proliferation is not of prognostic value.
— absence of fetal red blood cells and tissues unless with a twin gestation.
— volume of placental tissue often abundant >100 g.
— early moles: increasingly frequent with routine use of ultrasound examination. There can be a mixture of hydropic and non-hydropic villi or only lobulated villi, making diagnosis problematic. Look for branching and small sprouts of secondary villi, some invaginations in outline and trophoblast inclusions and a myxoid stroma with nuclear debris. Moderate trophoblast hyperplasia is also usually seen.

The vast majority regress but 10–15% develop persistent trophoblastic disease representing either incomplete removal of molar tissue, residual invasive mole within the myometrium or its vasculature, or choriocarcinoma.

Partial hydatidiform mole

— biparental; triploid 69XXY, a minority are trisomy.
— ± fetus (usually abnormal). Fetal death usually occurs around the 8th week, leaving only necrotic debris or a persistent fetal circulation with open vessels and nucleated red blood cells.
— a mixture of focal villous vesicular swelling with central cisterns and normal-sized villi.
— "Norwegian fjord" scalloped or dentate outline with trophoblast inclusions.
— circumferential/multifocal trophoblast hyperplasia, usually syncytiotrophoblast.
— volume of placental tissue normal.
— persistent disease in up to 1–2% of cases.

In molar change vesicles of 2–3 mm diameter are usually seen grossly.

Hydropic degeneration

— often trisomy or triploid.
— villi <2–3 mm and rounded.
— no cisterns.
— trophoblast polar in distribution and/or attenuated.

There is also a tendency to over-diagnose hydatidiform mole in ectopic tubal pregnancy due to the exuberant trophoblast that is associated with early non-molar gestational sacs.

Placental site reaction is a common localized phenomenon in curettings from abortions and must not be confused with gestational trophoblastic tumours. It comprises an exaggerated response of decidua, altered myometrial smooth muscle cells and intermediate trophoblast without myometrial destruction or invasion. It is usually associated with some immature villi. Placental site nodules or plaques are characterized by small size, circumscribed margins and hyalinization. Both are benign and do not require staging or follow-up.

Trophoblast is unlikely to be neoplastic if the last known pregnancy was recent, of short duration, aborted, and characterized by a mixture of villous and placental site trophoblast. The differential diagnosis between hydropic degeneration, partial and complete moles is often difficult and monitoring serum β sub-unit HCG levels is useful to ensure that they revert to normal in time. Trophoblastic disease is associated with persistently abnormal levels and if this is present after 60 days with a previous diagnosis of hydatidiform mole consideration is given to use of chemotherapy. Another differential diagnosis for choriocarcinoma is non-gestational carcinoma with trophoblast metaplasia, e.g. ovary, endometrium.

In curettage specimens trophoblast can be categorized as:

a. Villous trophoblast: the usual post abortion finding
b. Simple non-villous trophoblast: distinction between syncytio- and cytotrophoblast cannot be made and usually occurs after abortion
c. Suspicious non-villous trophoblast: no villi, a bilaminar arrangement of syncytio- and cytotrophoblast but no tissue invasion
d. Non-villous trophoblast diagnostic of choriocarcinoma: myometrial fragments with demonstrable invasion by bilaminar trophoblast.

Interpretation should be in the context of clinical, radiological and biochemical findings.

Flow cytometry can help to distinguish between a diploid complete mole and triploid partial mole, and between a triploid partial mole and non-molar diploid hydropic abortion. Cell proliferation markers (e.g. Ki-67) are strongly overexpressed in complete moles but are of limited practical value. The product of the maternally expressed gene CDKN1C, $p57^{KIP2}$ can be stained immunohistochemically. It shows high levels of nuclear expression in the cytotrophoblast and villous mesenchyme of partial moles and hydropic abortions but is absent in complete mole and may prove a useful adjunct to the main morphological criteria in the designation of molar pregnancies. It has not been found to be of use in identifying the type of causative pregnancy in established gestational trophoblastic tumours.

Urological Cancer

- Renal Cell and Renal Pelvis/Ureter Carcinoma
- Bladder Carcinoma
- Prostate Carcinoma
- Urethral Carcinoma
- Testicular Cancer
- Penile Carcinoma

29

Renal Cell and Renal Pelvis/ Ureter Carcinoma

1. GROSS DESCRIPTION

Specimen

— fine needle aspirate/needle core biopsy/partial nephrectomy/nephrectomy ± ureterectomy/radical nephrectomy (kidney, pelvis, perirenal fat out to Gerota's fascia, adrenal gland, and a length of ureter)/segmental ureterectomy.
— right/left.
— weight (g) and size (cm).
— length (cm) of attached ureter.
— adrenal gland: present/absent.
— up to one-third of renal cancers are asymptomatic and an incidental finding on radiological examination. The classic triad of flank pain, mass and haematuria is infrequent and usually indicates advanced disease. Weight loss and painless haematuria are perhaps the most frequent presenting complaints. Investigation for renal cell carcinoma is by abdominal ultrasound and CT scan, which can distinguish cystic and solid lesions and provide staging information on nodal, renal vein and inferior vena cava (IVC) involvement. Renal pelvic cancers are defined by retrograde pyelography and ureteropyeloscopy with cytological brushings and/or forceps biopsy. Needle biopsy is only done in a minority of renal cell cancers with extensive spread for the purposes of obtaining a tissue diagnosis as a prequel to palliative adjuvant or immunotherapy, and also to rule out a more treatable cause of the renal mass, e.g. malignant lymphoma. Most imaging-proven and kidney confined mass lesions require surgical resection and omitting an invasive needle biopsy avoids disrupting local anatomical structures and any risk of upstaging tumour. The mainstay of surgical treatment for renal cell carcinoma is radical nephrectomy but advances in preoperative imaging and staging have made partial nephrectomy an option for select patients, e.g. tumour <4 cm, tumour in a solitary kidney, or with a poorly functional contralateral kidney. Renal pelvis/ureter carcinoma requires nephrectomy with ureterectomy although endoscopic resection for early low grade lesions is also now being used.

Tumour

Site
— upper/lower pole, midzone, hilum, medullary, cortical, subcapsular, extracapsular, pelvic/peripelvic.
— single/multiple (satellite nodules in 5% of renal cell cancers) or bilateral (1%).
— most renal cell carcinomas are centred on the cortex, transitional cell carcinomas on the pelvis.

Size
— length × width × depth (cm) or maximum dimension (cm).

Appearance
— cystic/solid/lobulated: renal cell carcinoma.
— necrotic/haemorrhagic/yellow: renal cell carcinoma.
— circumscribed/tan/central scar: oncocytoma and chromophobe/papillary carcinomas.
— white/granular/scirrhous: sarcomatoid and collecting duct carcinomas.
— papillary/sessile/scirrhous: renal pelvis carcinoma.

Edge
— circumscribed/irregular.

Compression/infiltration structures
— perinephric fat, capsule, cortex, medulla, pelvis, peripelvicalyceal fat (renal sinus), adrenal gland, renal vein.

2. HISTOLOGICAL TYPE

Renal malignancy of childhood is not discussed.

Renal cell carcinoma (Heidelberg/WHO classifications)

Adenocarcinoma
— 90% of cases.
— clear cell: 70% of cases. Solid/trabecular/alveolar/tubuloacinar/cystic patterns with a prominent sinusoidal vascular stroma and areas of haemorrhage. Glycogen and fat-rich clear to eosinophilic granular cytoplasm and variable nuclear morphology.
— papillary: 10–15% of cases. Potentially multifocal, bilateral and familial arising on a background of precursor papillary adenoma(s). Formerly termed chromophil carcinoma. Encapsulated, with solid and tubular patterns but at least 50–70% of the tumour area is papillary with stromal aggregates of foam cells, focal psammomatous microcalcification and haemorrhage. The commonest renal carcinoma in dialysis patients.
  type 1—basophilic cuboidal cell, uniform bland appearance and more often multifocal
  type 2—eosinophilic columnar cell with nuclear (pseudo) stratification.

— chromophobe: 3–5% of cases. Solid and nested patterns with a perinuclear halo, clear to flocculent cytoplasm (positive with Hale's colloidal iron and alcian blue), prominent ("koilocyte-like") cytoplasmic membranes and "wrinkled" hyperchromatic nuclei.
— collecting duct: 1% of cases, located in the medulla with irregular tubules and papillae in a desmoplastic stroma, hob-nail cells and nuclear stratification. Aggressive although a rare low-grade variant exists.
— sarcomatoid: 1–2% of cases with a solid/scirrhous appearance and fibrosarcomatous/MFH-like spindle cell (± giant cell) morphology and usually with high nuclear grade. May occur either as a major or minor component with the other main subtypes, and also renal pelvic carcinoma, and is regarded as an indication of disease progression and a poorly differentiated or high-grade form of them with poor prognosis rather than a specific entity in its own right. Pale/scirrhous area within an otherwise usual renal cell carcinoma should be preferentially sampled for histology. Infiltrating transitional cell carcinoma of the renal pelvis has a similar appearance.
— mixed: about 10% of cases show mixed differentiation.
— unclassified: 5–10% of cases do not fit into any distinctive category.
— on a spectrum with and forming a differential diagnosis for the eosinophilic variants of well-differentiated (grade 1) renal cell carcinoma and chromophobe carcinoma is benign renal oncocytoma. A circumscribed, tan/brown lesion with a central radial scar comprising sheets, tubules and small nests of cells, with abundant eosinophilic cytoplasm and a central, small round nucleus, set in a variably oedematous stroma. Forming 3–5% of renal neoplasms, its cytoplasm is rich in mitochondria. It is excluded in favour of a designation of renal cell carcinoma by necrosis, mitoses, clear cells, spindle cells, papillary areas, gross vascular invasion or gross extension into perirenal fat. It is occasionally multifocal and bilateral with associated oncocytomatosis.

Neuroendocrine carcinoma
— carcinoid/small cell/large cell: rare.
— NSE, chromogranin/synaptophysin/CD56 positive.
— small cell carcinoma may also arise from the pelvic mucosa as part of a transitional cell carcinoma secondarily involving the kidney parenchyma.

Renal pelvis/ureter carcinoma

Transitional cell (urothelial) carcinoma
— ± calculi or a history of analgaesic nephropathy with renal papillary necrosis.
— single/multifocal.
— 20% of upper renal tract neoplasms.
— 30% of cases are low grade and papillary giving hydroureter/hydronephrosis with a non-functioning kidney and a radiological

filling defect in the pelvis/ureter. The other 70% of cases are high grade and a mixture of papillary and sessile lesions. The latter can infiltrate the medulla and cortex with a scirrhous gross appearance and squamoid or spindle cell morphology.

Squamous cell carcinoma
— calculi/infection/squamous metaplasia of the pelvic mucosa.
— mostly high-grade and locally advanced/metastatic at presentation. Prognosis is poor.
— mixed: as part of a high-grade transitional cell carcinoma (40% of cases).

Adenocarcinoma
— pure: tubulovillous/mucinous/signet ring cell/papillary non-mucinous. Adjacent pyelitis cystica/glandularis secondary to chronic inflammation, e.g. calculi.
— mixed: as part of a high-grade transitional cell carcinoma.

Sarcomatoid carcinoma
— spindle cell carcinoma with high nuclear grade and cytokeratin positive. May be combined with foci of usual transitional cell carcinoma.

Metastatic carcinoma
— often small and bilateral (50%).
— direct spread: cervix, prostate, bladder (distal ureter), gut, retroperitoneal metastases, e.g. lung and breast.
— distant spread: lung, malignant melanoma (skin), breast, stomach, pancreas, ovary, testis.

3. DIFFERENTIATION/GRADE

Renal cell carcinoma
Well/moderate/poor/undifferentiated, or Grade 1/2/3/4.
Differentiation and nuclear grade are not infrequently heterogeneous within a lesion. The malignant cell typically has a low nuclear/cytoplasmic ratio.

Nuclear grade (Fuhrman)

1. Round, uniform, 10 μm, nucleoli absent
2. Slightly irregular, 15 μm, nucleoli visible
3. Moderately to markedly irregular, 20 μm, large nucleoli
4. Bizarre multinucleated forms, ≥20 μm, prominent nucleoli, clumped chromatin.

Grades 2 (35%) and 3 (35%) account for the majority of cases. Prognostic significance of nuclear grade also varies according to tumour type, e.g. metastatic papillary renal carcinoma is usually high-grade whereas metastatic clear cell renal carcinoma is often of low nuclear grade.

Transitional cell carcinoma
WHO I/II/III.
Low grade (WHO I) or high grade (WHO II/III).
For further discussion of classification of urothelial neoplasms see Chapter 30.
For non-transitional pelviureteric cancers: well/moderate/poor/undifferentiated, or Grade 1/2/3/4.

4. EXTENT OF LOCAL TUMOUR SPREAD

Border: pushing/infiltrative.
Lymphocytic reaction: prominent/sparse.

Capsule, perirenal fat

The capsule is often elevated and compressed by the pushing and lobulated margin of renal cell adenocarcinoma and this must be distinguished from actual histologically proven invasion of perirenal fat by tumour cells (pT3a). In this respect the capsule and fat should not be stripped from the kidney prior to sectioning it, otherwise the cortex/capsule/fat interface is lost. Extension to the renal sinus (peripelvicalyceal fat) should be actively examined for, as it is particularly susceptible to vascular invasion.

Pelvis, ureter

Renal pelvic transitional cell carcinoma is not infrequently multifocal (40%) with concurrent ureteric lesions ± bladder tumour. The adjacent urothelium is often abnormal, ranging from hyperplasia through dysplasia to carcinoma in situ.

Renal vein

Renal cell adenocarcinoma has a propensity for venous invasion, and involvement of the renal vein or its segmental (muscle containing) branches should be identified grossly at specimen dissection with subsequent histological confirmation.
The TNM classification applies to renal cell, renal pelvis and ureter carcinomas.

Renal cell carcinoma

pT1 tumour ≤ 7 cm in greatest dimension, limited to the kidney
  a. ≤4 cm
  b. 4 cm < tumour ≤7 cm
pT2 tumour > 7 cm in greatest dimension, limited to the kidney
pT3 tumour invades:
  a. perinephric fat* or adrenal gland†

*Includes renal sinus (peripelvicalyceal fat) and †direct invasion of the ipsilateral adrenal gland. Contralateral adrenal gland involvement is rare (pM1). Gerota's (renal) fascia is retrorenal and prerenal with invasion beyond the latter sometimes resulting in peritoneal involvement (pT4). Renal sinus involvement has been noted to be the commonest site of extrarenal extension (pT3) and vascular involvement, and correlates with tumour type, grade and size. Its evaluation, which has been frequently omitted in the past, can upstage disease if involved.

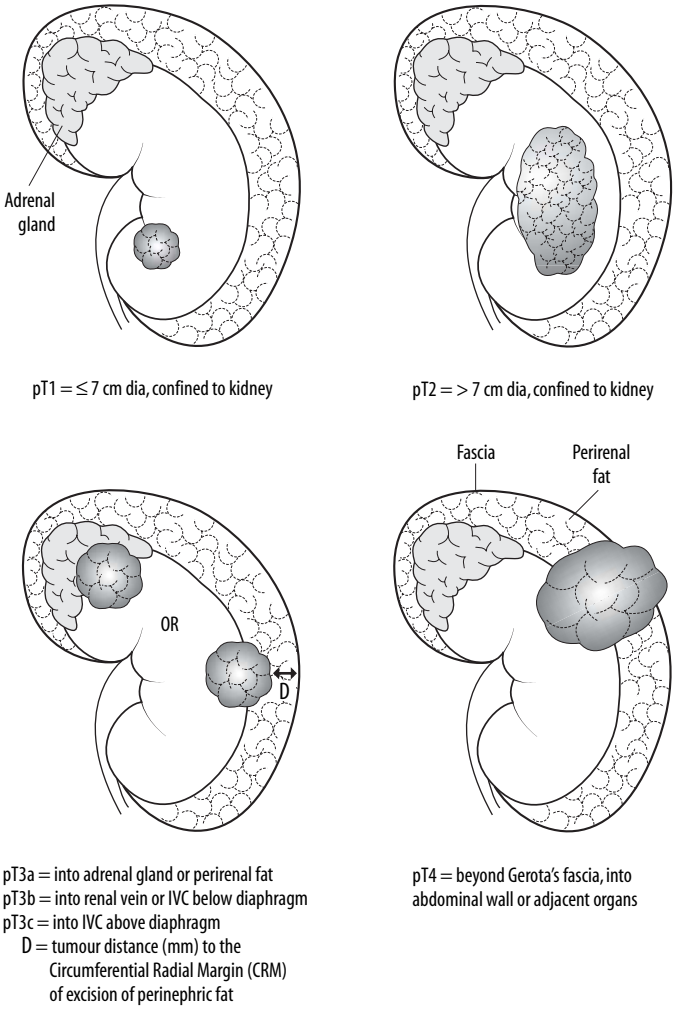


FIGURE 29.1. Renal cell carcinoma.

b. grossly into renal vein, IVC or its wall below diaphragm
c. grossly into IVC or its wall above diaphragm

pT4 tumour invades beyond Gerota's fascia.

Involvement of renal vein and ipsilateral adrenal gland is seen in 10% and 5% of cases, respectively. Metastases occur in the lung, skeleton and skin and to almost any site where they can mimic primary clear cell

tumour in the involved organ, e.g. thyroid, ovary. Preferential metastatic sites are seen with various subtypes of carcinoma, e.g. papillary carcinoma has fewer lung metastases and more lymph node deposits than clear cell carcinoma, and chromophobe carcinoma tends to spread to liver.

Pelvis/ureter carcinoma

pTis	carcinoma in situ
pTa	papillary non-invasive
pT1	tumour invades subepithelial connective tissue
pT2	tumour invades muscularis propria
pT3	tumour invades beyond muscularis into peripelvic fat or renal parenchyma (pelvis) tumour invades beyond muscularis into periureteric fat (ureter)
pT4	tumour invades adjacent organs, or through the kidney into perinephric fat.

For ureter adjacent organs include parietal peritoneum. Ureteric pT3 disease is prognostically equivalent to pT4 renal pelvis tumour.
Pelvis/ureter carcinoma: single/multifocal lesion(s); hydroureter/hydronephrosis.

For the purposes of TNM considered as a single organ and synchronous pelviureteric lesions are classified according to the highest pT category, e.g. pT2(m). In contrast, synchronous renal pelvis and bladder cancers are classified independently.

50% present as superficial disease and 50% are deeply invasive (pT2 or beyond).

5. LYMPHOVASCULAR INVASION

Present/absent.
Intra-/extratumoral.
Renal cell carcinoma has a tendency to involve the main renal vein, while infiltrating pelvic transitional cell carcinoma often shows invasion of small lymphovascular channels in the medulla and cortex. However, it can also subsequently involve the renal vein. In renal cell carcinoma prognostically adverse renal sinus (peripelvicalyceal) fat macro- and microvascular invasion should also be sought and identified.

6. LYMPH NODES

Site/number/size/number involved/limit node/extracapsular spread.

Regional nodes: hilar, abdominal para-aortic, paracaval (ureter-intrapelvic). A regional lymphadenectomy will ordinarily include a minimum of eight lymph nodes, although it is often not performed in UK surgical practice. A few nodes may be found at the renal hilum and, occasionally, individual operatively suspicious nodes will be submitted. Separate dissection of the paraaortic and paracaval nodes gives optimal staging information in that a pNX specimen has worse 5-year survival (61%) than a pN0 nephrectomy (74%) implying inaccurate downstaging.

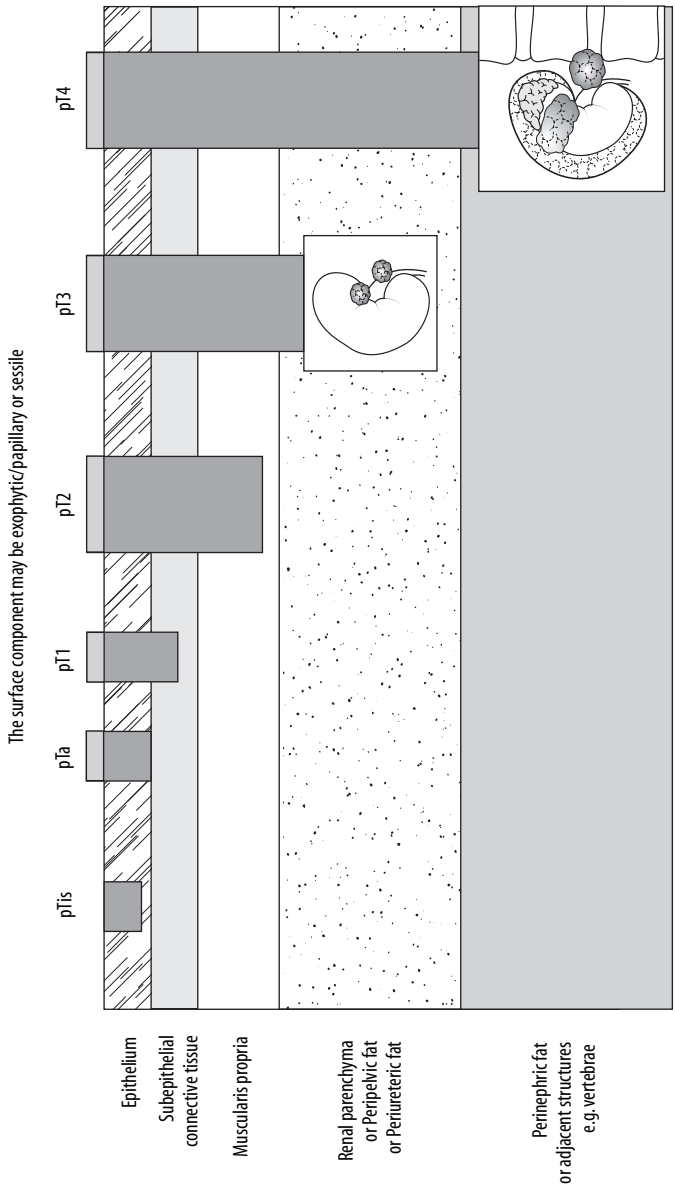


FIGURE 29.2. Renal pelvis and ureter carcinoma.

Renal cell carcinoma

pN0 no regional lymph node metastasis
pN1 metastasis in a single regional node
pN2 metastasis in more than one regional node.

Regional node metastases occur in 10–15% of cases and are associated with an adverse prognosis.

Pelvis/ureter carcinoma

pN0 no regional lymph node metastasis
pN1 single regional node metastasis ≤2 cm
pN2 single regional node metastasis >2 cm to 5 cm, multiple ≤5 cm
pN3 regional node metastasis >5 cm.

Regional node metastases occur in 5–10% of renal pelvic urothelial carcinomas.

7. EXCISION MARGINS

Distances (mm) to the distal ureteric limit, renal vein limit, perirenal fat and periureteric resection margins. Also the renal parenchyma resection limit in partial nephrectomy.

8. OTHER PATHOLOGY

There is a degree of correlation between gross morphology, cell type and architectural patterns in renal cell carcinoma, e.g. clear cell is lobulated, yellow with areas of haemorrhage and non-papillary, while chromophobe and chromophil tumours are circumscribed and tan coloured, the latter being papillary in character. Sarcomatoid carcinoma is usually pale and scirrhous in appearance with a differential of invasive pelvic transitional cell carcinoma, while renal clear cell adenocarcinoma may become totally cystic with only small residual mural nodules of viable tumour. Multilocular cystic renal cell carcinoma has a good prognosis.

Chromosomal analysis characterizes various morphological subtypes, e.g. papillary vs. non-papillary renal carcinoma. Cytogenetically papillary tumours show a trisomic gain on chromosomes 7 and 17 rather than the 3p13 deletion of usual renal cell carcinoma. Chromophobe carcinomas can be hypodiploid with multiple monosomies. Primary ureteric carcinoma is associated with HNPCC.

Von Hippel Lindau (VHL) syndrome has an increased incidence (40–50%) of renal cell carcinoma, as do acquired (e.g. long-term dialysis) and congenital polycystic disease (5–10%). VHL has cysts with variable single cell, hyperplastic or solid clear cell epithelial lining. The renal carcinoma tends to be multiple and there are cysts elsewhere in kidney, liver and pancreas, phaeochromocytoma and cerebellar haemangioblastoma.

Occasionally renal cell carcinoma can spontaneously regress and also be host to cancer metastasizing to within cancer, particularly from lung carcinoma. Other associated characteristics are fever, hepatic dysfunction, hypercalcaemia, hypertension (secretion of renin), polycythaemia

(secretion of erythropoietin) and hormonal effects (secretion of ACTH-like substance).

Amyloid can be present in the renal interstitium adjacent to renal cell carcinoma and systemic in distribution. Glomerulonephritis is also an association.

Xanthogranulomatous pyelonephritis (XGP) and malakoplakia can mimic pelvic/renal cell carcinoma grossly and on needle biopsy. XGP comprises CD68 positive macrophages lacking cytokeratin positive epithelial cells, while malakoplakia shows eosinophilic macrophages with von Kossa or PAS stainable Michaelis-Gutmann bodies. Other differential diagnoses on biopsy can be

- renal papillary adenoma: circumscribed, <0.5 cm, papillae with fine fibrovascular cores ± tubules and a single layer of uniform cuboidal eosinophilic/basophilic cells. Associated with renal cell carcinoma, papillary renal cell carcinoma and oncocytoma and may be multiple
- metanephric adenoma/adenofibroma: circumscribed, small uniform cells in crowded tubules and papillae forming glomeruloid bodies. Scanty intervening stroma with psammoma bodies but areas of fibrosis in the adenofibroma variant. It is EMA negative, unlike its differential diagnosis papillary renal carcinoma
- oncocytoma: see above
- angiomyolipoma: epithelioid variant (HMB-45 positive)
- multicystic nephroma: simple cysts lined by flat cuboidal to columnar hob-nail cells and intervening fibrous stroma ± muscle, cartilage and focal blastematous elements (partially differentiated nephroblastoma).

A solid clear cell lesion of any size (even if <3 cm) should be regarded as a renal carcinoma with a 3-cm dimension considered a threshold for metastatic potential. Adenoma is reserved for small papillary, or metanephric lesions as defined above.

Percutaneous FNAC is usually avoided but can give a diagnosis of simple renal cysts vs. cystic or solid renal cell carcinoma. Carcinoma is cellular, shows nuclear atypia with a low nuclear/cytoplasmic ratio, nucleolar enlargement and variable fat/glycogen positive cytoplasmic vacuolation. Pelvic carcinoma also shows cytological features of malignancy. FNAC has a more defined role in investigation of suspected metastatic disease.

Immunophenotype

Renal clear cell carcinoma is typically cytokeratin (AE1/AE3, CK8,18)/EMA/vimentin/CD10/N-cadherin positive, variable for RCC ab and negative for CK7/E-cadherin/Ber EP4/MOC 31.

Papillary renal cell carcinoma is CK 7/RCC ab/Ber EP4/EMA positive, and variable for CD10/MOC 31.

Chromophobe carcinoma is CK7/EMA/E-cadherin/MOC 31/BerEP4 positive and CD10/RCC ab/vimentin/N-cadherin negative.

Sarcomatoid carcinoma retains vimentin and focal keratin positivity.

Oncocytoma is variable for CK7 and CD10/MOC 31 negative.

Thus the various combinations of immunoprofiles can aid morphology in distinguishing the histological subtypes, although there can be a marked overlap of expression between categories. Oncocytoma vs. chromophobe carcinoma (MOC 31), renal clear cell carcinoma vs. oncocytoma and chromophobe carcinoma (CK7, CD10, N/E-cadherins, BerEP4, MOC 31), and renal clear cell carcinoma vs. papillary renal cell carcinoma (CK7, CD10, RCC ab, BerEP4). Renal clear cell carcinoma (CD10 positive/melan-A, inhibin negative) may also be discriminated from adrenal gland carcinoma, which has a converse immunophenotype.

RCC ab and CD10 mark proximal tubules, MOC 31 and BerEP4 distal tubules. CD10 is also positive in renal pelvic transitional cell carcinoma, particularly high-grade and stage tumours but its expression is inversely related to tumour grade in renal clear cell carcinoma.

Renal cell carcinoma is treated by partial or heminephrectomy (nephron sparing surgery) or radical nephrectomy depending on the size and location of the tumour. Partial nephrectomy ranges from tumour enucleation to heminephrectomy with part of the pelvicalyceal system and related overlying perirenal fat. Radical nephrectomy removes an entire kidney, en bloc adrenal gland, perirenal fat out to Gerota's fascia and variable lengths of hilar vessels and ureter. Indications for nephron sparing surgery are: tumour <4 cm diameter, location at a renal pole and of non-papillary type. Renal pelvis/ureter carcinoma usually requires nephrectomy with ureterectomy, often including resection of the ureteric orifice because of multifocality and involvement of its terminal, vesical (intramural) portion. Solitary distal ureteric lesions may be treated by segmental ureterectomy with ureteral reimplantation. Ureterectomy with endoscopic resection of small low-grade, superficial pelvic lesions may be used as a renal-sparing procedure when there is solitary kidney or poor renal function. Occasionally a pelvic carcinoma may be found in a radical nephrectomy supposedly removed for a diagnosis of renal cell carcinoma. This leaves the issue of potential metachronous disease in the residual ureter and secondary ureterectomy may be considered. Resection of solitary pulmonary metastases can be of benefit for renal cell and renal pelvic cancers.

Prognosis

Up to 30% of renal cell carcinomas present with spread beyond the kidney and 10% involve renal vein with a tendency to solitary distant metastases, e.g. lung, skin and bone with pathological fracture. Chromophobe and papillary carcinomas have a better prognosis than equivalent grade and stage renal clear cell carcinoma, while sarcomatoid and unclassified cancers are worse (94%, 86%, 76%, 35% and 24% 5-year survivals, respectively). Overall 5-year survival is 70% relating to tumour grade, type (e.g. grade III/IV and sarcomatoid lesions are aggressive), vascular invasion and stage, although cure is possible even with main vessel involvement. Chemotherapy is largely ineffective, although when combined with immunotherapy it may have a role to play in nodal or widespread disease.

pT1 60–80%
pT2 40–70%
pT3 10–40%
pT4 5%.

Carcinoma of the renal pelvis/ureter is predominantly transitional cell in type with occasional squamous cell, adenocarcinoma and sarcomatoid carcinoma. Typically there are multifocal, synchronous pelvi-ureteric (25%) and bladder (15%) lesions with a 50% risk of subsequent metachronous tumours at these sites. About 30% are low grade and 70% high grade with 50% representing superficial disease and 50% deeply invasive (pT2 or beyond). The latter can form poorly differentiated nests, sheets and cords of tumour in a desmoplastic stroma often assuming a squamoid appearance. Retrograde involvement of medullary collecting ducts (mimicking adenocarcinoma) and lymphovascular invasion are not uncommon. Low-grade superficial lesions are of good prognosis but critical invasion of or beyond ureteric muscle coat, renal pelvic wall or parenchyma results in 5-year survival rates of 35%.

9. OTHER MALIGNANCY

Lymphoma/leukaemia

- usually secondary to systemic/nodal disease and present in up to 50% of cases, and potentially bilateral. If established as a primary lymphoma it is usually large B cell in type. Diffuse tumour cell permeation or tumour masses
- lymphoma is occasionally associated with renal cell carcinoma
- post-transplant lymphoproliferative disorder.

Leiomyosarcoma, liposarcoma, malignant fibrous histiocytoma, rhabdomyosarcoma

— all rare and important to exclude more common diagnoses, i.e. sarcomatoid renal cell carcinoma and primary retroperitoneal sarcoma with secondary renal involvement.

Angiomyolipoma with malignant transformation

— tuberous sclerosis in 30%, multifocal (30%), bilateral (15%).
— HMB-45/melan-A/CD117/desmin positive spindle cells with variable cellularity and pleomorphism (giant/epithelioid cells) ± mitoses, mature fat and thick-walled vessels.
— capsular invasion and nodal disease may be seen and is often regarded as multicentricity rather than malignancy. Rarely true malignant change can occur (epithelioid variant).
— prone to catastrophic/potentially fatal haemorrhage particularly if >4 cm.
— rarely associated with concurrent renal cell carcinoma.
— a PEComa (perivascular epithelioid cell tumour).

30
Bladder Carcinoma

1. GROSS DESCRIPTION

Specimen

— urine cytology/bladder washings/cystoscopic biopsy/transurethral resection bladder (TURB)/ cystectomy/cystourethrectomy/cystoprostatectomy (including seminal vesicles)/cystoprostatourethrectomy/anterior or total exenteration (including uterus and adnexae ± rectum).
— weight (g) and size (cm).
— length (cm) of ureters and urethra.
— bladder cancer commonly presents with symptoms of painless haematuria and investigation is by urinary cytology, cystoscopy and biopsy. Cytology is good at designating high-grade papillary, in-situ and invasive urothelial neoplasia but poor at separating low-grade papillary lesions from reactive atypia and cellular changes associated with calculi, in-dwelling catheters, recent instrumentation and post-therapy changes. Biopsy is with "cold" cup forceps or a small diathermy loop, the advantage of the former being good preservation of histological detail. Flexible cystoscopy is easier for the patient and allows a wide field of vision but rigid cystoscopy with a larger lumen allows instrument access for transurethral resection of superficial bladder tumours with diathermy to the base (TURBT). Deep biopsy of the muscularis propria is important staging information in invasive tumours and may be submitted separately by the urologist. Further staging is by a combination of endoluminal ultrasound, CT and MRI scan. Carcinoma in situ is usually treated by topical chemotherapy (mitomycin) or immunotherapy (bacille Calmette–Guérin (BCG) therapy) or resected by TURB if localized. Widespread disease may necessitate radical surgery. Superficial urothelial cancer confined to the mucous membrane is resected transurethrally with submission of multiple fragments and follow-up by cystoscopy. Adjuvant intravesical therapy is used for high-grade or recurrent disease. Muscle-invasive tumours require radical surgery with cystectomy ± in continuity prostatectomy/urethrectomy and regional lymphadenectomy, and in the female cystourethrectomy or an anterior exenteration.

Tumour

Site
— fundus/body/trigone/neck/ureteric orifices.
— anterior/posterior/lateral (right or left).
— single/multifocal.
— diverticulum.

Size
— length × width × depth (cm) or maximum dimension (cm).

Appearance
— papillary/sessile/ulcerated/mucoid/keratotic/calcification.
— bladder mucosa: erythematous/oedematous (carcinoma in situ).

Edge
— circumscribed/irregular.

2. HISTOLOGICAL TYPE

Transitional cell (urothelial) carcinoma
— 90% of cases.
— usual type: papillary or sessile.

variants with deceptively benign features:

— microcystic type: intraurothelial microcysts containing protein secretions mimicking cystitis cystica.
— nested type: uniform cell nests in the lamina propria mimicking florid Von Brunn's nests but with an irregular margin and look for muscle invasion. Potentially aggressive.
— micropapillary type: resembles ovarian serous papillary carcinoma. Associated with stromal retraction artefact mimicking lymphovascular invasion. Also shows true LVI and is a high-grade tumour.
— inverted type: architecturally similar to inverted papilloma but has WHO II/III cytology. Look for muscle invasion.
— also clear cell, plasmacytoid, lipid cell, with pseudosarcomatous stroma (see below), trophoblastic cells (HCG positive) or prominent lymphoid infiltrate (lymphoepithelioma) variants.

Squamous cell carcinoma
— 5% of cases.
— classical/verrucous/basaloid/sarcomatoid, i.e. the same range of tumours as encountered in the upper aerodigestive tract.
— old age and associated with calculi, schistosomiasis or diverticulum and chronic infection. Prognosis is poor with a 13–35% 5-year survival and two-thirds are pT3/pT4 at presentation.

Adenocarcinoma
— the common cloacal embryological origin of bladder and rectum highlights the range of glandular differentiation that can be seen in the bladder mucosa.
— 2% of bladder malignancy.
— enteric, mucinous (colloid), signet ring cell, clear cell (mesonephroid), ex villous adenoma, or adenocarcinoma not otherwise specified (NOS).
— can arise either from intestinal metaplasia/cystitis glandularis (60%), extrophy, diverticulum or bladder dome wall urachal remnants (30%). Usually muscle invasive and of poor prognosis (particularly signet ring cell carcinoma).

Transitional cell (urothelial) carcinoma with mixed differentiation
— squamous cell carcinoma/adenocarcinoma components are seen in 20–30% of high-grade invasive transitional cell carcinomas emphasizing a capacity for divergent differentiation.

Spindle cell carcinoma
— "sarcomatoid carcinoma" or carcinosarcoma.
— old age. Large and polypoid with a poor prognosis (50% dead within 1 year). There may be a recognizable in-situ or invasive epithelial (transitional, glandular, squamous or undifferentiated) component and cytokeratin/vimentin positive spindle cells with varying stromal differentiation, from non-specific fibrosarcoma-like to specific heterologous, mesenchymal differentiation, e.g. rhabdomyosarcoma, chondrosarcoma, osteosarcoma.

Small cell carcinoma
— primary or secondary from lung. CAM5.2/synaptophysin/CD56 positive. Aggressive with early metastases to nodes, liver, bone and peritoneum. May be pure or mixed with other in-situ or invasive bladder cancer subtypes and there is coexistent prostatic disease in 50% of cases.
— large cell neuroendocrine carcinoma also occurs rarely.

Undifferentiated carcinoma
— no specific differentiation and a high-grade tumour.

Malignant melanoma
— primary or secondary (commoner).
— note there can be spread to bladder from a primary urethral lesion.

Metastatic carcinoma
— metastases should be considered in any bladder tumour with unusual histology, e.g. adenocarcinoma or squamous cell carcinoma. Knowledge of a previous positive history and comparison of morphology are crucial. Metastatic disease in the bladder is usually solitary.

— direct spread from adjacent pelvic organs (>70% of cases): prostate, cervix, uterus, anus, rectum, colon. To distinguish primary adenocarcinoma from secondary colorectal carcinoma look for an origin at the dome from mural urachal remnants, or areas of adjacent mucosal intestinal metaplasia/cystitis glandularis in a primary lesion. A previous positive history on cervical smear/biopsy or endometrial sampling raises the possibility of a primary gynaecological tract malignancy.

Prostatic cancer is PSA/PSAP positive but CK7/CK20/34βE12 negative, which is the converse of bladder cancer. Note that some poorly differentiated or metastatic prostate cancers stain more strongly with polyclonal rather than monoclonal PSA with the potential for a false-negative result using only the latter.

— distant spread: breast, malignant melanoma, lung, stomach.

3. DIFFERENTIATION/CYTOLOGICAL GRADE

Flat, papillary and invasive urothelial neoplasia are graded separately. There are several classification options, although in the UK the WHO 1973 scheme remains in favour rather than the more recent WHO/ISUP 1998 consensus and WHO 1999 classifications due to concerns about their reproducibility. In general, they are based on the degree of cytoarchitectural abnormality characterized by increasing nuclear atypia, hyperchromasia and crowding with up-regulated proliferative and mitotic activity.

Flat urothelial neoplasia: comprises urothelial dysplasia (mild/moderate/severe) on a spectrum with, and severe dysplasia equating to, carcinoma in situ (CIS). Urologists will follow up a diagnosis of dysplasia but initiate treatment for CIS which may entail BCG immunotherapy, intravesical chemotherapy or surgery. Dysplasia and CIS (syn: low- and high-grade intraurothelial neoplasia, respectively) are to be distinguished from urothelial hyperplasia and regenerative atypia which can be encountered in a range of conditions, e.g. cystitis, calculi, an indwelling urinary catheter or post chemo-/radiotherapy. In addition to morphological clues, dysplasia/CIS overexpresses p53 and Ki-67 with strong, diffuse CK20 staining, whereas non-neoplastic urothelium tends to show only basal layer proliferative activity and CK20 staining of surface umbrella cells.

Papillary urothelial neoplasia: papillary urothelial lesions with a spectrum of minimal to marked cytoarchitectural abnormalities ranging from the very rare benign transitional cell papilloma covered by normal urothelium to the commonplace transitional cell carcinomas WHO I/II/III (G1/G2/G3). A WHO I/G1 carcinoma is the least disordered, being a low-grade lesion with <5% risk of progression to invasion. A WHO III/G3 tumour is the most anaplastic, being high-grade with a 15–40% risk of progression. Thus a papillary neoplasm is typed, graded and assessed for the presence of underlying invasion with comment on the absence or presence of dysplasia or CIS in the represented flat mucosa in the rest of the sample. A comparison of the classifications is given in Table 30.1.

Table 30.1 Classification of papillary urothelial neoplasms

WHO 1973	Transitional cell papilloma		Transitional cell carcinoma	
	WHO 0/G0	WHO I/G1*	WHO II/G2†	WHO III/G3†
WHO/ISUP 1998	Urothelial papilloma	Papillary urothelial neoplasm of low malignant potential (PUNLMP)	Low-grade urothelial carcinoma	High-grade urothelial carcinoma
WHO 1999	Urothelial papilloma	Papillary urothelial neoplasm of low malignant potential (PUNLMP)	Urothelial carcinoma WHO I/G1 WHO II/G2	WHO III/G3

*Low-grade disease.
†High-grade disease.
Note that the columns are not discrete categories or directly transferable but represent a spectrum of cytoarchitectural abnormalities. Transitional cell (urothelial) papilloma can be exophytic or inverted in type.

Invasive urothelial neoplasia: well/moderate/poor, or WHO I/II/III (G1/2/3). Note that WHO III invasive urothelial carcinoma often assumes a squamoid appearance in addition to actual mixed squamous or glandular differentiation (20–30% of cases).

Non-urothelial invasive neoplasia: well/moderate/poor/undifferentiated, or Grade 1/2/3/4. For squamous cell carcinoma based on keratinization, cellular atypia and intercellular bridges, and, for adenocarcinoma, on the tumour percentage gland formation (well/G1: >95%; moderate/G2: 50–95%; poor/G3: <50%). Signet ring cell adenocarcinoma is high grade (G3).

4. EXTENT OF LOCAL TUMOUR SPREAD

Border: pushing/infiltrative.
Lymphocytic reaction: prominent/sparse.

The TNM classification applies to urinary bladder carcinomas (non-invasive and invasive) and also papillary urothelial (transitional cell) neoplasm of low malignant potential (see above).

pTis carcinoma in situ: potential multifocal urinary tract field change
pTa papillary non-invasive
pT1 invasion of subepithelial connective tissue
pT2a invasion of superficial muscle (inner half)
pT2b invasion of deep muscle (outer half)
pT3 invasion of perivesical fat:
  a. microscopically
  b. extravesical mass (macroscopically)
pT4 invasion of:
  a. prostate, uterus, vagina
  b. pelvic wall, abdominal wall.

Direct invasion of distal ureter is classified by the depth of greatest invasion in any of the involved organs.

Invasive bladder cancer with associated in-situ change extending into prostatic urethra or duct epithelium is classified according to the depth of bladder wall invasion and comment on the in-situ changes noted by use of a suffix, e.g. pT2b (ispu) for prostatic urethral involvement.

Involvement of prostatic urethra or stroma by invasive disease is pT4a, as is small or large intestine, peritoneum covering the bladder and seminal vesicles.

Superficial tumours are regarded as either pTa or pT1 and are often histological grade I or II. Formal substaging of pT1 bladder tumours is not usually done but comment should be made on the degree of invasion, e.g. focal or extensive, above/at/below muscularis mucosae (pT1a: cores of papillae; pT1b: lamina propria; pT1c: below muscularis mucosae).

Deeply (muscle) invasive tumours are pT2 or pT3 and more often grade III. They are prognostically adverse, requiring more radical treatment and assessment of invasion of the detrusor layer of muscularis propria is of crucial importance in their designation. As well as invasion of the

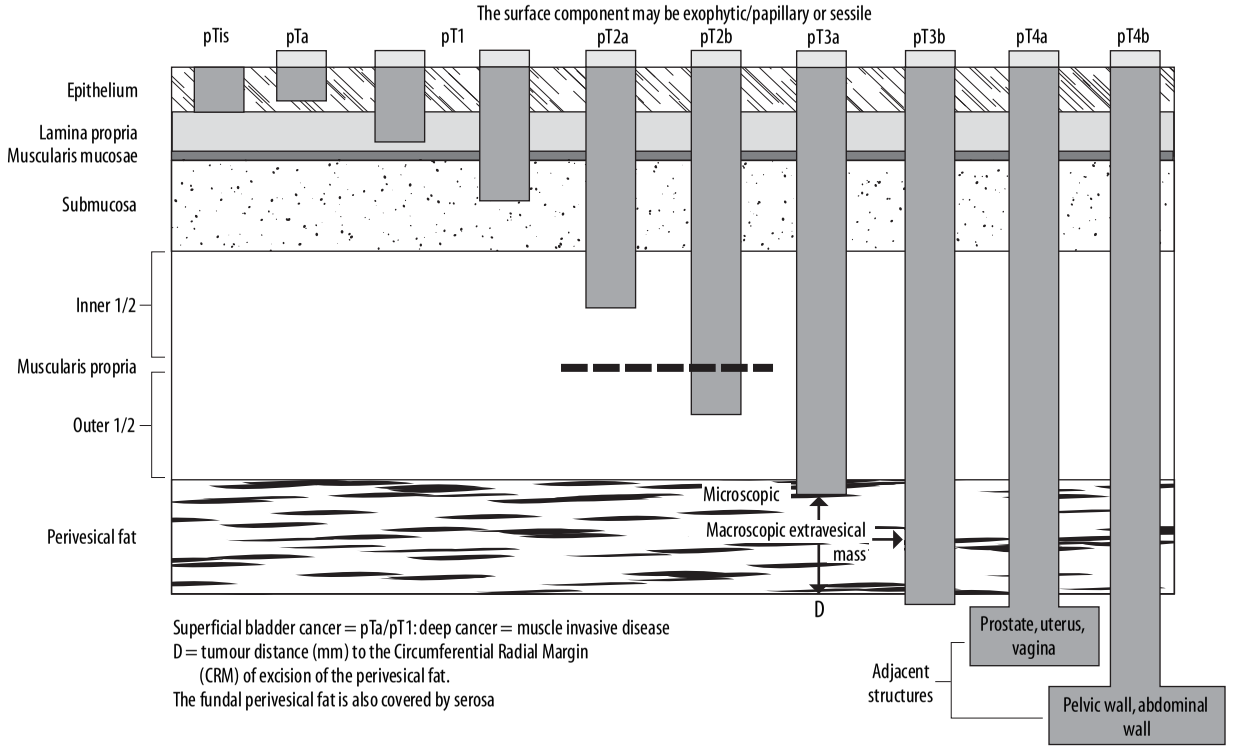


FIGURE 30.1. Urinary bladder carcinoma.

bladder wall, urothelial cancer can extend into the bladder neck, prostate, urethra and seminal vesicles. Because of this, urethral biopsy is done in staging patients with CIS or high-grade invasive disease and en bloc prostatourethrectomy favoured at the time of cystectomy.

5. LYMPHOVASCULAR INVASION

Present/absent.

Intra-/extratumoral.

Invasion into the lamina propria may result in prominent retraction artefact spaces around tumour cells and nests mimicking lymphovascular invasion. This phenomenon is particularly prominent in micropapillary carcinoma. For true vascular involvement identify an endothelial lining with adherent tumour and red blood cells. Endothelial markers (CD31, CD34) may be of use. Vascular invasion is associated with an increased rate of recurrence.

6. LYMPH NODES

Site/number/size/number involved/limit node/extracapsular spread.

Regional nodes: pelvic nodes below the bifurcation of the common iliac arteries.

pN0 no regional lymph nodes metastasis
pN1 metastasis in a single regional node ≤ 2 cm
pN2 metastasis in a regional node > 2 cm but ≤ 5 cm or multiple regional nodes each ≤ 5 cm
pN3 metastasis in a regional node > 5 cm.

Nodal metastases are present in 25% of invasive TCCs. Common sites of distant metastases are lungs, liver, bone and CNS.

7. EXCISION MARGINS

Distances (mm) to the limits of the urethra, ureters, circumferential perivesical fat margin and fundal serosa, and the inferior resection limit of the bladder wall in a partial cystectomy. Note also the presence of any dysplasia/CIS at the ureteric and urethral limits.

8. OTHER PATHOLOGY

Diagnostic criteria for TCC

Carcinoma in situ (CIS)

— flat urothelium of variable thickness (3–20 layers).
— marked cytological abnormality of usually (but not always) the whole epithelial thickness of either large cell (±pleomorphism) or small cell types.
— note unusual patterns such as the Pagetoid variant, or clinging CIS resulting from dyscohesion and shedding of cells.
— CIS equates to severe dysplasia and is by its nature a high-grade lesion.
— present adjacent to invasive carcinoma in 50–60% of cases.
— beware of overcalling dysplasia or in-situ change, as normal urothelium often partially denudes on biopsy, leaving a thin covering of basal cells which can then appear hyperchromatic.

— note that a biopsy diagnosis of dysplasia with no previous history may progress to CIS or invasive malignancy in up to 19% of cases over the course of several years.

Papillary TCC
— >7 cell layers thick.
— papillae with fine stromal cores which are not true lamina propria (a distinguishing feature from the broad oedematous cores of polypoid cystitis).
— variable nuclear grade of abnormality.

Growth pattern

Papillary, exophytic
— the vast majority of cases.

Sessile
— tends to be associated with high-grade lesions.

Endophytic and non-invasive, or invasive
— differentiate from inverted papilloma (covering of normal urothelium, no atypia or mitoses, inversion of the epithelial layers).
— non-invasive lesions have an intact, round basement membrane and no desmoplastic or inflammatory stromal response and often represent a complex crypt pattern to the lesion base or extension of malignant epithelium into Brunn's nests. Invasive endophytic lesions can have a rounded deep border with no inflammatory reaction, making assessment of invasion difficult—look for atypical urothelium present in relation to muscularis propria.

Microinvasion
— characterized by single cells, irregular spicules or nests of atypical urothelium budding into or lying separately in the superficial lamina propria often associated with stromal oedema, retraction artefact or a loose fibroblastic response. Deeper invasion comprises irregular cell nests separated by variably desmoplastic submucosa or detrusor muscle bundles. Histological interpretation can be partially compromised by TURBT diathermy distortion.

Pathological predictors of prognosis
— number of tumours/multifocality: both within the bladder and extravesical, e.g. ureters and renal pelvis.
— size of tumour.
— depth of invasion.
— histological grade.
— coexistent carcinoma in situ/dysplasia adjacent to or away from the tumour are markers of higher risk for recurrence and progression.
— progression of grade and stage with time.
— poor initial response to chemo-/radiotherapy.

Additional comments

Biopsies

Assess material from: the base (for pT stage), and adjacent and distant mucosa (for pTis). Clear distinction between superficial and deep muscle cannot be made on biopsy material (unless submitted separately by the clinician), so that muscle-invasive carcinoma should be reported as at least pT2a in depth. The muscle bundles should be coarse indicating the detrusor layer or muscularis propria rather than the fine fibres of the poorly defined lamina propria. Note that fat may also be present in the lamina propria and between muscle coat bundles and does not necessarily mean invasion of perivesical tissue. This designation is reserved for complete assessment of the cystectomy specimen. Biopsies from other lesions that can mimic a papillary neoplasm are polypoid cystitis, nephrogenic adenoma, follicular cystitis, cystitis cystica, malakoplakia, villous adenoma and inverted papilloma. Although the latter is benign, a small minority can be multifocal and recurrent and difficult to distinguish from urothelial carcinoma with an inverted pattern. Mimics of a solid urinary neoplasm are previous biopsy site reaction, inflammatory pseudotumour, amyloid, endometriosis, sarcoma, extrinsic and metastatic carcinoma.

Resection blocks

— urethral limit: transverse section.
— ureteric limits: transverse section.
— prostate, seminal vesicles: not infrequently there is concurrent, undiagnosed prostatic adenocarcinoma which requires separate typing, Gleason score and TNM staging.
— normal bladder: lateral walls, dome, trigone.
— tumour and wall: one section per cm of tumour diameter to show the deepest point of mural invasion.

Post-operative necrobiotic granuloma

— post-TURP fibrinoid necrosis with palisading histiocytes. Biopsy site reaction to previous TURB often shows prominent neofibrotic granulation tissue, focal dystrophic calcification and a foreign body giant cell response which may be associated with diathermy coagulum. The giant cells can be epithelioid and "pseudocarcinomatous" in appearance and cytokeratin/CD68 staining may be necessary to help distinguish from residual invasive urothelial carcinoma.

Post-operative spindle cell nodule and inflammatory myofibroblastic tumour (IMFT)/pseudosarcomatous fibromyxoid tumour

These are myofibroproliferative processes histologically resembling sarcoma. Spindle cell nodule is small (5–9 mm) and has a history of recent genitourinary tract instrumentation. It comprises a proliferation of cytologically bland spindle cells in which normal mitoses are readily seen and it occurs at the operative site. IMFT occurs de novo, can be several centimetres in diameter or larger and forms a polypoid mass. The atypical myofibroblastic proliferation is associated with prominent

inflammation and granulation tissue-type vasculature. Mitoses can be seen, but are not prominent or abnormal. Both lesions are usually benign and must be distinguished from sarcoma, although some cases of IMFT have been reported to recur and even progress with local infiltration. Cytokeratin is positive in spindle cell nodule but often negative in IMFT (a useful discriminator from spindle cell carcinoma); actin and desmin are variably positive (40–80%). IMFT can be ALK positive.

Diverticulum ± calculus: squamous cell carcinoma.

Immunophenotype

Transitional cell carcinoma is positive for cytokeratins 7, 8, 18 and 20, CEA, uroplakin III, CA19-9, Leu M1 and Lewis X antigen. Overexpression of p53 correlates with the likelihood of progression in superficial disease. A useful panel is 34βE12/CK7/CK20/p53 positive: PSA/PSAP negative with the converse for poorly differentiated prostatic carcinoma, which helps to clarify the nature of poorly differentiated carcinoma at the bladder base.

Treatment of bladder TCC is usually by transurethral resection and cystoscopic follow-up. High-grade (pT1G3) or refractory superficial disease (i.e. confined to the mucous membrane) may also need radiotherapy and/or intravesical chemotherapy/BCG. The latter are also useful for TCC in situ. Non-responsive superficial or deep (muscle-invasive) cancer necessitates surgery. In follow-up, note that intravesical agents such as mitomycin lead to urothelial atypia and these changes must not be confused with dysplasia or carcinoma in situ. The nuclei are focally enlarged and have a "smudged" chromatin appearance rather than the angular, ink blank hyperchromasia of in-situ change. BCG often results in inflammation and superficial non-caseating granulomas but bacilli are usually not seen. A range of other post-therapy changes can be seen with systemic chemotherapy, radiotherapy, laser and photodynamic therapy. Urachal-related adenocarcinoma at the bladder dome may be considered for a partial cystectomy with resultant preservation of urinary function.

Prognosis

Muscle-invasive cancer often starts as carcinoma in situ or a flat/sessile rather than a papillary lesion and relates strongly to histological grade (WHO I = 2% invasive; WHO III = 40% invasive). Invasive cancer will develop in up to 30–50% (or more) of patients with untreated carcinoma in situ but 85–90% 5-year survival rates can be achieved by radical surgery which is also targeted at multifocal field change in the urothelium (bladder, prostatic ducts, urethra, ureters, seminal vesicles). Up to 80% of urothelial carcinomas are non-invasive at the time of presentation and although tumour recurrence is common (single lesion 30–45%, multiple 60–90%), tumour progression (10%) relates strongly to histological grade, tumour size, non-tumour dysplasia of bladder mucosa and depth of invasion. Overexpression (>20% of tumour cells) of Ki-67, p53 and Her-2 may also be other prognostic indicators. Five-year survival rates also vary according to these parameters:

Transitional cell carcinoma	Superficial invasion	
	Grade I	70%
	Grade III	60%
	Deep muscle invasion	40–55%
Squamous cell carcinoma		15%
Adenocarcinoma		15–35%

As can be seen, squamous cell carcinoma and adenocarcinoma are of worse prognosis.

9. OTHER MALIGNANCY

Lymphoma/leukaemia
— usually secondary to systemic disease.
— primary lymphoma varies from low-grade MALToma with indolent behaviour to diffuse large B-cell lymphoma. Leukaemic involvement is seen in 15–30% of cases.

Carcinoid tumour
— rare.

Phaeochromocytoma
— young women. Paragangliomatous nested pattern of cells with eosinophilic cytoplasm and variable nuclear features. Chromogranin positive with S100 positive sustentacular cells.
— local recurrence and metastases can occur in about 10% of cases. Histology does not reliably predict behaviour.

Leiomyosarcoma
— commonest sarcoma in adults, bladder dome, infiltrates muscle.
— nuclear atypia mitoses and tumour necrosis: some are extensively myxoid.
— desmin/h-caldesmon positive.

Other sarcomas
— rhabdomyosarcoma, malignant fibrous histiocytoma, osteosarcoma: all rare and must exclude sarcomatoid carcinoma (carcinosarcoma).

Rhabdomyosarcoma
— embryonal variant in children, sarcoma botryoides.
— cellular subepithelial cambium layer with a loose myxoid zone and cellular deep zone ± rhabdomyoblasts. Desmin/myo D1/myogenin positive.

Choriocarcinoma and yolk sac tumour
— choriocarcinoma: exclude urothelial carcinoma with trophoblastic differentiation.
— yolk sac tumour: rare; childhood.

31
Prostate Carcinoma

1. GROSS DESCRIPTION

Specimen

— fine needle aspirate/needle core biopsy (18 gauge)/transurethral resection (TUR) chippings/radical prostatectomy (including seminal vesicles) and regional lymphadenectomy.
— weight (g) and size (cm).
— number and length of cores (mm).
— symptomatic prostatic cancer is often indicative of widespread disease with lumbar pain as a result of bone metastases. It may also present with prostatism but is frequently detected because of an elevated serum PSA with digital rectal examination (DRE) either as part of a screening programme or a family practitioner's well man check-up. Further investigation comprises transrectal ultrasound (TRUS) to identify classical tumour-related hypoechoic areas. Because 70% of prostatic cancer is present posteriorly and peripherally this is coupled to per rectum clinical or TRUS-directed needle core biopsies (clinical: right/left/transitional zone; TRUS: sextant/3 samples each side aimed at apex/mid/base regions). Recent evidence shows that a percentage of cancers are isoechoic and an extended 10-core biopsy regime has been advised. The resultant fine biopsy cores need careful handling, wrapping and painting with alcian blue prior to processing to allow their visualization at the block cutting stage. Otherwise initial block trimming may result in loss of diagnostic tissue. Blocks are cut through at least three histological levels and the intervening ribbons kept pending any subsequent need for immunohistochemistry. Microscopic assessment is at low power looking for abnormalities of glandular architecture and medium to high power to confirm cytological features of malignancy. The biopsy report should indicate which biopsy site is positive, the Gleason tumour grade, the number of positive cores and percentage of involved tissue. It may be possible to comment on other staging information, e.g. spread into extracapsular fat or neurovascular bundles, or involvement of seminal vesicles. Another indication for prostatic biopsy is a rising serum PSA after radiotherapy or brachytherapy for a previously proven cancer. Reasons for a repeat biopsy are an insufficient index biopsy, features suspicious but not

diagnostic of malignancy, high-grade PIN and a rising serum PSA after a negative biopsy. Treatment of prostatic cancer is age, fitness, grade and stage-dependent ranging from watchful waiting to hormonal therapy (androgen deprivation) for focal and locally advanced or metastatic disease, respectively. Metastatic disease is assessed by radioisotope bone scan while CT scan and MRI scan have limited sensitivity for local spread. Radical prostatectomy is aimed at younger patients (50–65 years) with low to modest elevations in serum PSA who are more likely to have gland-confined disease and negative surgical margins. It is an operation with significant morbidity and side-effects (e.g. incontinence, impotence), some of which may be avoided by a selective nerve-sparing procedure, although this can have implications for the completeness and tumour clearance of margins. An equivalent alternative with fewer complications is radical radiotherapy and there is also increasing use of brachytherapy (radioactive seed implants) or cryotherapy of the tumour and its bed. Preoperative combination therapy can downsize tumour while post-operative radiotherapy and/or chemotherapy are based on the Gleason component and sum scores, margin status and extracapsular disease. Prostatic chippings piece-meal resect the periurethral and central zones and TURP is performed in two main situations: a. in patients with benign hypertrophy of the medial aspect of the gland who have persistent troublesome prostatism (urinary frequency, hesitancy, dribbling) that is refractory to medical therapy or who develop acute urinary retention, or b. TURP channel re-do in a patient with known cancer and significant prostatic symptoms. In the former incidental cancer may be detected histologically (8% of cases) and the significance of this is then interpreted in light of the patient's serum PSA and clinical staging.

Tumour

Site

— inner (transitional)/outer (central and peripheral) zones. The transitional zone surrounds the proximal urethra and the central zone is posterior to it. The peripheral zone occupies 70% of the gland in a horseshoe shape around its posterior and lateral aspects.
— medial/lateral (right or left) lobes. These are not defined anatomical structures but relate to clinically palpable masses on per rectum examination. For the purposes of TNM staging the gland is notionally divided into right and left lobes about a mid-point sagittal plane
— posterior/subcapsular.
— the majority of carcinomas are posterior and peripheral with multicentricity present in up to 75% of cases.

Size

— length × width × depth (cm) or maximum dimension (cm).
— tumour volume (cm^3). Derived by outlining and calculating the area of tumour in each slide and then multiplying by the mean block

thickness (the anteroposterior diameter divided by the number of coronal slices). The volume is the sum total for all the blocks/slides. Alternatively, a quicker method is to outline the tumour in each slide, lay them out on the bench and estimate the total percentage area involved, e.g. 60%. Knowing the gland volume (AP × width × depth) the tumour volume is presumed to be 60% of it, assuming even tumour distribution throughout each block. Clinicians vary in the use of these data but pragmatically they gives an indication of the risk of extracapsular disease. It is also useful for correlation with serum PSA and TRUS assessment along with tumour site location. However, its importance is far outweighed by that of consistent Gleason scoring and assessment of the capsule and margin status. Given the heterogeneity of tumour distribution within the prostate, volume estimates are more accurate based on whole gland serial slices and processing. This can mean 40–50 slides for a small gland using routine blocks. Two alternatives are: a. whole mount sections that reduce the block numbers and allow easier assessment of lobar tumour distribution, or b. a sampling strategy to include the base and apical margins, seminal vesicles, all posterior sections and a mid-slice of the anterior prostate on either side. In needle biopsy and TURP specimens the number of cores and percentage of chippings involved are routinely given in the surgical histopathology report.

Appearance
— soft/firm.
— pale/yellow/granular.
Similar changes are seen in tuberculosis, infarction, granulomatous prostatitis and acute and chronic prostatitis, i.e. tumour is difficult to define macroscopically and histological assessment is necessary.

Edge
— circumscribed/irregular.

2. HISTOLOGICAL TYPE

Peripheral acinar/duct origin

Adenocarcinoma with acinar, diffuse single cell infiltration, papillary, cribriform, comedo patterns

- usual types (>90–95% of cases).
- acini are usually small to medium in size and can be rounded or angular in contour. Diagnosis is made at low-power magnification on the basis of a gland-rich haphazard infiltrative pattern in comparison with and between ducts of adjacent benign prostatic tissue. Medium to high power can then confirm the lack of an epithelial bilayer and nuclear characteristics of malignancy (enlargement/angularity/membrane folds/nucleolar prominence). Luminal crystalloids may also be present. Cribriform and comedo patterns resemble intraductal carcinoma and can be difficult to distinguish from high-grade PIN (Prosta-

tic Intraepithelial Neoplasia), but again are architecturally too ductal-rich compared with adjacent tissues. Diagnostic pitfalls are large gland, atrophic and pseudohyperplastic variants of carcinoma which can resemble post atrophic or benign hyperplastic prostate. Occasionally clear cell or foamy gland adenocarcinoma is encountered to be distinguished from cytokeratin negative/CD68 positive aggregates of xanthomatous histiocytes. Notably these well differentiated carcinoma variants are negative for the basal layer cytokeratin marker 34βE12.

Mucinous adenocarcinoma

— distinguish from secondary colorectal or bladder cancer by a relevant past history and also usually CK7/CK20 negative. Variable PSA/PSAP expression.
— ≥25% of the tumour area is intra-/extracellular mucin.
— fewer bone metastases and less hormone/radioresponsive than usual prostatic carcinoma.

Signet ring cell adenocarcinoma

— rare; distinguish from secondary gastric or colorectal cancer by a relevant past history and also usually CK7/CK20 negative. Variable PSA/PSAP expression.
— ≥25% of the tumour area is signet ring cells, usually coexisting with other poorly differentiated carcinoma and of poor prognosis.

Basal cell carcinoma

— a morphological continuum from typical through florid basal cell hyperplasia/adenoma to carcinoma with infiltrative edges, stromal desmoplasia, comedonecrosis and adenoid cystic-like differentiation. 34βE12 positive and a tumour of variable malignant potential.

Undifferentiated, small cell type carcinoma

— CAM5.2/synaptophysin/CD56 positive. Immunonegative cases are classified as poorly/undifferentiated prostatic carcinoma.
— lung small cell carcinoma analogue.
— primary or secondary from lung, pure or mixed (25%) with usual prostatic carcinoma ± an associated bladder component.
— aggressive: sometimes inappropriate ACTH/ADH secretion.
— carcinoid tumour is rare. Up to 33% of usual prostatic carcinomas can show neuroendocrine differentiation on immunohistochemistry and this is usually of no prognostic significance.

Adenosquamous/squamous carcinoma

— rare and poor prognosis. Exclude squamous metaplasia due to infarction or hormone therapy, or spread from bladder or anal cancer.
— up to 50% may arise in prostate cancer patients after endocrine or radiotherapy.

Lymphoepithelial carcinoma

— analogous to nasopharyngeal carcinoma.

Sarcomatoid/spindle cell carcinoma
— syn. carcinosarcoma or metaplastic carcinoma.
— cytokeratin positive spindle cells with variable malignant stromal mesenchymal differentiation which is usually homologous ± heterologous elements (bone, cartilage, striated muscle).
— older men, variable prognosis.

Central (large) duct origin

Periurethral duct adenocarcinoma
— old age and polypoid/villous or infiltrative on cystoscopy. Has a more advanced stage at presentation and is aggressive. May be associated with a diverticulum.
— variable papillary, cribriform and endometrioid patterns (uterine carcinoma analogue). Prostate specific antigen/prostatic acid phosphatase (PSA/PSAP) positive, ±oestrogen sensitive.
— associated Paget's disease of the prostatic urethra.
— exclude secondary renal clear cell carcinoma if mesonephroid or hob-nail clear cell in type.

Transitional cell carcinoma
— 2% of prostatic cancers.
— arise from the transitional cell lining of the prostatic urethra or proximal periurethral ducts.
— usually high grade with extension into ducts, central comedonecrosis ± adjacent stromal invasion, the presence of which is the strongest prognostic indicator.
— exclude spread from a bladder transitional cell carcinoma.

Mixed acinar/large duct types and adenocarcinoma/transitional cell carcinoma

Metastatic carcinoma
— direct spread: bladder (in 40% of radical cystoprostatectomies for bladder cancer), colorectum, anus, retroperitoneal sarcoma.
— distant spread: kidney, lung (squamous carcinoma), malignant melanoma.

3. DIFFERENTIATION/GRADE
Well/moderate/poor/undifferentiated, or Grade 1/2/3/4.

— well/G1 = Gleason sum score 2–4; moderate/G2 = Gleason 5–6; poor/G3 = Gleason 7–10.
— 50% of cases show heterogeneity of tumour grade.
— signet ring cell carcinoma is poorly differentiated (grade 3) and small cell carcinoma undifferentiated (grade 4). Specific carcinoma variants can be allocated a Gleason score, e.g. mucinous adenocarcinoma (pattern 4), small cell carcinoma and signet ring cell (pattern 5) but scoring is more applicable to usual type prostatic adenocarcinoma.

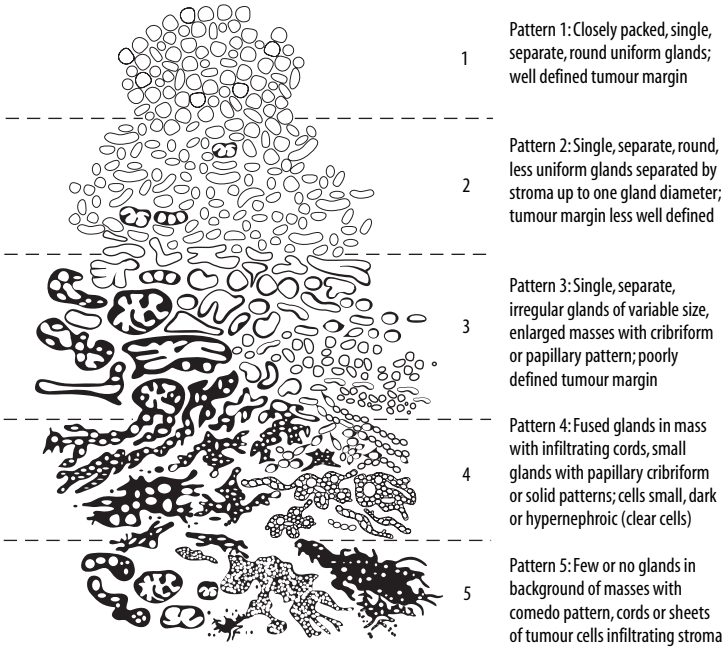


FIGURE 31.1. Gleason score in prostatic carcinoma. (Gleason DF. The Veterans Administration Cooperative Urologic Research Group: Histologic grading and clinical staging of prostatic carcinoma. In: Tannenbaum M (ed) Urologic pathology: the prostate. Philadelphia: Lea and Febiger, 1977.).

Gleason score for usual prostatic adenocarcinoma

The Gleason system proposes that any given prostate carcinoma may show one or several of five histological glandular architectural patterns ranging from the lowest grade (grade 1) to the highest grade (grade 5). Taking the two predominant patterns one can arrive at a score (e.g. 2 +3 = 5; 3 + 4 = 7) which has prognostic significance. The following rules apply:

(a) choose the two predominant patterns where more than two are present
(b) when there is only one pattern, double it, e.g. 3 + 3 = 6
(c) in limited samples (e.g. needle biopsy, TUR chippings) where there are more than two patterns and the worst grade is neither the predominant nor the second most predominant pattern, choose the main pattern and the highest grade. For example, if grade 3 is 60%, grade 1 is 30% and grade 4 is 10%, the score is 3 + 4 = 7. Note that due to sampling error and crush artefact, needle biopsy samples can underestimate the Gleason score compared with the subsequent resection specimen and scoring is subject to observer variability. A useful tip when assessing Gleason score is: f for fusion and 4, i.e. packed glands

with elimination of intervening stroma. Cribriform (pattern 4) and comedo (pattern 5) areas may also be present. Where there are multiple needle biopsies or foci in a prostatectomy with different Gleason scores the score of the least differentiated areas should be recorded. Urological oncologists also like to know the component parts of the sum score (i.e. 3 + 4 = 7) as management may be based on the percentage worst element.

Note that a needle biopsy positive for prostatic adenocarcinoma is usually of at least Gleason pattern 3, i.e. small, angular individual glands infiltrating stroma. Gleason pattern 1 or 2 cancers comprise larger, uniform glands in circumscribed nodules more easily appreciated in centrally located TURP specimens. Useful guides to Gleason scoring of prostatic adenocarcinoma are found at http://pathology2.jhu.edu/gleason and from the 2005 ISUP Consensus Conference (Epstein et al. Am J Surg Pathol 2005; 29:1228–1242).

4. EXTENT OF LOCAL TUMOUR SPREAD

Border: pushing/infiltrative.
Lymphocytic reaction: prominent/sparse.
Weight of chippings or length of cores and proportion (%) or number involved. For a focal lesion give a maximum dimension (mm).
Apex of gland, urethral limit, proximal bladder limit, capsule and margins, seminal vesicles.

The TNM classification applies only to prostatic adenocarcinomas. Transitional cell carcinoma of the prostate is classified as a urethral tumour.

pT1 clinically inapparent tumour not palpable or visible by imaging
- T1a incidental histological finding in ≤5% of tissue resected
- T1b incidental histological finding in >5% of tissue resected
- T1c identified by needle biopsy (e.g. because of elevated PSA)

pT2 tumour confined within the prostate
- T2a involves one-half of one lobe or less
- T2b involves more than one-half of one lobe but not both
- T2c involves both lobes

pT3 tumour extends through the prostatic capsule
- T3a extracapsular extension (unilateral or bilateral)
- T3b invades seminal vesicle(s)

pT4 tumour is fixed or invades neighbouring structures: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall.

Invasion into but not beyond prostatic apex or capsule is pT2. The capsule is a condensation of smooth muscle and collagen-rich soft tissue around the prostate but with no clear fascia. It can be difficult to define in a prostatectomy specimen for the purposes of assessing extracapsular disease (tumour in fat or neurovascular bundles beyond the contour of the prostate) and sometimes has to be visually extrapolated from more obvious adjacent areas in any given slide. Completeness of the capsule

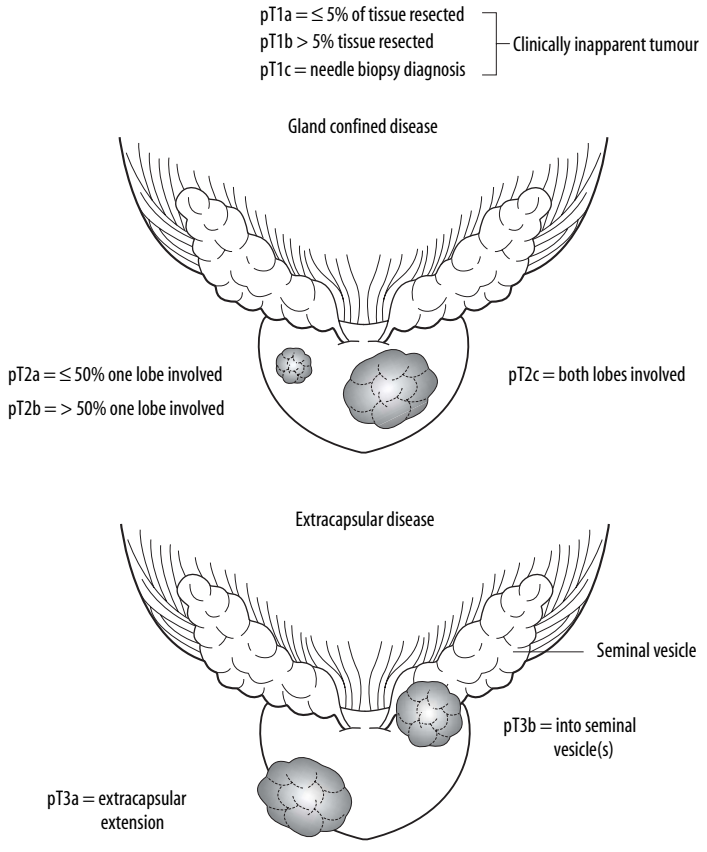


FIGURE 31.2. Prostatic carcinoma.

also depends on patient anatomy, surgical expertise and choice of operative technique, e.g. a nerve-sparing procedure. Extracapsular extension can be described as focal or extensive (adverse prognosis).

Due to the inferoposterior approach of per rectal needle biopsy there may be representation of extracapsular and seminal vesicle tissues which should be assessed for invasion (=pT3). Note that fat and muscle can also be intraprostatic and involvement on its own in a needle biopsy does not necessarily imply extracapsular disease. However, tumour in perineural spaces in neurovascular bundles in fat is an indicator of extracapsular spread, as is infiltration around ganglion cells. Occasionally benign acini may be present in perineural spaces. Seminal vesicle involvement (pT3b) is defined as invasion of its smooth muscle wall and not just the surrounding connective tissue between it and the

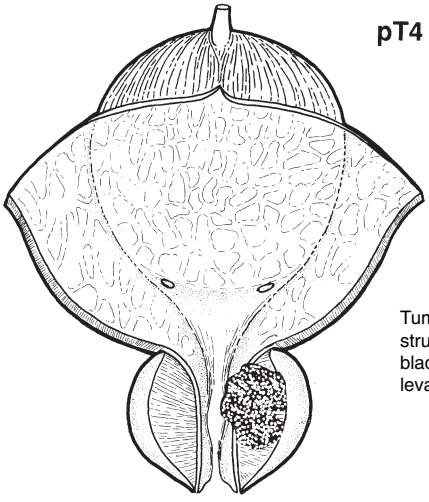


FIGURE 31.3. Prostatic carcinoma.

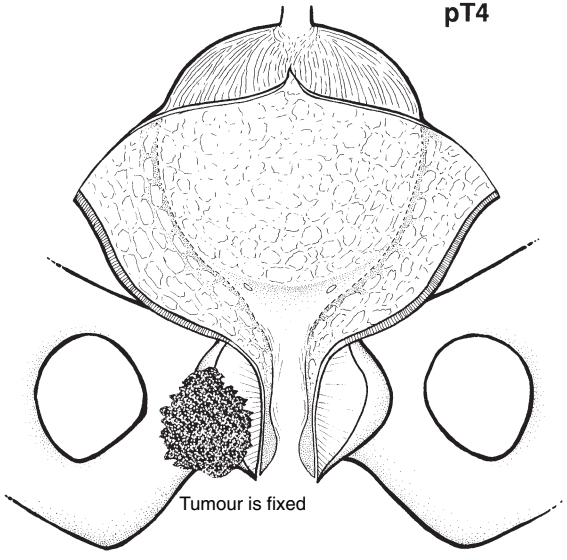


FIGURE 31.4. Prostatic carcinoma.

prostate. This is not to be confused with similar looking ejaculatory duct type epithelium which is oriented to loose, vascular connective tissue. Advanced disease manifests spread into seminal vesicle, prostatic urethra and bladder. Presentation can be by an anterior rectal mass or stricture and PSA staining of rectal biopsy material is of use. "Frozen pelvis" is a clinical term meaning tumour extension to the pelvic wall(s) with fixation and is designated pT4. Optional descriptors are pT4a (bladder neck, external sphincter, rectum) and pT4b (levator muscles, fixed to pelvic wall). Note that the normal prostatic apex may incorporate some striated muscle fibres and cancer lying in relation to these does not necessarily imply extraprostatic disease.

Histological cancer in TURPs performed within 2 months of each other should have a pT1a or1b designation based on the sum total of carcinoma over both specimens. In a prostatectomy specimen where part of the capsule is missing, the pT designation can be accurately assigned only if the tumour is clearly surrounded by non-tumorous prostatic tissue.

5. LYMPHOVASCULAR INVASION

Perineural and lymphovascular space: while its positive predictive value is low, perineural invasion can be an indicator of potential extraprostatic extension and associated with prostatic carcinoma of higher Gleason score and volume. Microvascular invasion is also a possible predictor of tumour progression.

Present/absent.

Intra-/extratumoral.

6. LYMPH NODES

Site/number/size/number involved/limit node/extracapsular spread.

Regional nodes: pelvic nodes below the bifurcation of the common iliac arteries.

pN0 no regional lymph node metastasis
pN1 metastasis in regional lymph node(s).

Lymph node metastases are present in up to 10–30% of radical prostatectomy specimens relating to tumour stage, volume, differentiation and serum PSA levels. Some patients with high-risk disease defined by serum PSA level and biopsy tumour grade may have frozen section assessment of regional nodes prior to carrying out radical surgery. Nodal tumour volume or maximum diameter is an index of metastatic potential. The next commonest sites of metastases are bone (osteoblastic in character) and lung, and occasionally testis. Occult primary disease can present with metastases to unusual sites, e.g. pleura, bronchus, mediastinal and supraclavicular lymph nodes. Bronchial biopsy and aspiration cytology coupled with PSA immunoreactivity can be useful in these circumstances, particularly as the pattern can mimic other cancers, e.g. secondary colonic adenocarcinoma.

7. EXCISION MARGINS

Distances (mm) to the circumferential surgical resection margins, proximal bladder and distal urethral limits.

A margin is involved if tumour is present histologically at the covering of ink. If close to but not touching the ink it is negative. Occasionally assessment is not clear-cut and margin status is deemed to be equivocal. A positive margin does not necessarily alter the stage or mean pT3a disease, as the gland may have been excised at or internal to the capsule at this particular point. The apex and posterolateral margins are unduly susceptible to positive margins. Proximally a pT4 designation generally requires gross tumour in bladder detrusor muscle rather than just microscopic involvement of the bladder neck. The proximal and distal limits are transverse sectioned and then serially sliced perpendicular to this to demonstrate satisfactorily their actual outer surfaces.

Capsular and marginal invasion are strong indicators of extraprostatic disease and potential progression. Note that the prostatic capsule is poorly defined particularly at the base and apex of the gland, where there is a paucity of fat and extraprostatic extension is hard to ascertain. A positive margin may be designated R1 by TNM, i.e. incomplete resection with residual microscopic disease (e.g. pT3 (R1)) and it is significantly associated with PSA relapse (see below).

8. OTHER PATHOLOGY

Extent of high-grade prostatic intraepithelial neoplasia (HGPIN) and location (usually peripheral as in carcinoma): HGPIN has malignant cytology (i.e. nuclear/nucleolar enlargement) within preserved ducts ± focal disruption of the basal cell layer with high molecular weight 34βE12 cytokeratin stain. Its intraductal architectural patterns are tufting, micropapillary, cribriform and flat. About 40–50% are associated with concurrent or subsequent adenocarcinoma. Its presence in biopsy cores or chippings indicates the need to process more tissue and for clinical reassessment and follow-up. HGPIN does not cause a significant rise in serum PSA or form a palpable mass. It is a histological finding and is not detected by ultrasound. Its prevalence and extent are decreased by androgen deprivation therapy. A differential diagnosis is with invasive cribriform adenocarcinoma. Low-grade PIN is not reported due to variation in its observer reproducibility and uncertainty as to its significance as a precursor lesion.

High-molecular-weight cytokeratin antibody 34βE12 reacts with the basal cells of prostatic glands in benign conditions but is negative in adenocarcinoma. Important morphological markers of adenocarcinoma are: nuclear/nucleolar enlargement, absence of the basal cell layer, perineural invasion (especially if circumferential and intraneural) and loss of gland architecture. Luminal crystalloids may also be seen. A putatively positive immunomarker for prostatic adenocarcinoma is alpha-methylacyl CoA racemase (AMACR/P504S).

34βE12 and AMACR/P504S are of use in difficult differential diagnoses of prostatic adenocarcinoma, i.e. HGPIN, post-atrophic hyperplasia, sclerosing adenosis, atypical adenomatous hyperplasias (benign cytology within an abnormal glandular architecture at the edge of hyperplastic nodules), nephrogenic adenoma, mesonephric remnants, various hyperplasias (transitional/squamous/cribriform) and Cowper's glands.

Overdiagnosis of seminal vesicle epithelium as malignant should also be borne in mind: look for cytoplasmic lipofuscin pigment and characteristic cytoarchitectural appearances. Basal cell hyperplasia/adenoma are also 34βE12 positive. About 3% of needle biopsy specimens show small acinar proliferation suspicious but not diagnostic of malignancy. This can be due either to the presence of small atypical glands without fully developed cytoarchitectural features of malignancy, or to a very limited number (<3) with overtly malignant features, i.e. quality and quantity (the "Q^2 of positive diagnosis"). Interpretation must be viewed in light of the clinical findings, e.g. a rising serum PSA. Further biopsy may be necessary.

Radiotherapy and hormonal treatment (androgen deprivation therapy) produce glandular atrophy with nuclear apoptosis, cytoplasmic vacuolation and stromal fibrosis. These may lead to underestimation of tumour bulk in post-treatment resection specimens and difficulty in deriving a Gleason score. These treatment-related changes along with better diagnosis of early disease can result in the minimal residual or "vanishing cancer" phenomenon in prostatectomy specimens. In such cases the needle biopsy material should be reviewed to verify the primary diagnosis and future management based on its prognostic indicators. Conversely, lack of morphological response to neoadjuvant therapy has adverse prognosis.

Mucinous and signet ring cell carcinoma have to be distinguished from secondary colorectal carcinoma. Immune markers PSA and PSAP will be positive in 95% of primary prostatic carcinomas but may be negative in mucinous prostatic cancers. If immune markers are negative, absence of any obvious primary elsewhere is important in designation as a primary prostate lesion. Note that PSAP can also be positive in rectal carcinoid tumours and anal carcinoma. PSA can also stain some ovarian, salivary gland, skin and breast cancers.

Periurethral duct carcinoma has a worse prognosis than prostatic carcinoma of usual type but may also be oestrogen sensitive. It has cribriform or papillary patterns and is PSA positive. Many coexist with typical acinar prostatic carcinoma and may be related to it.

Prostatic carcinoma has a tendency to be peripheral and posterior in distribution, allowing a diagnosis to be made in a significant number of cases by multiple per rectal needle biopsies. Multiple sextant biopsies can also act as a guide to the distribution and extent of the lesion. Biopsies should be examined histologically through multiple levels (at least 3) to detect focal lesions. Measurement of the maximum tumour dimension (mm) should be given. Small foci (<3 mm) in one core may represent true focal cancer or a sampling issue and not representative of the whole lesion. Small areas of tumour in a biopsy may indicate small volume disease in the radical prostatectomy but the considerable overlap that exists in individual patients poses considerable limitations on this as a predictor. The weight of TURP chippings determines the number of blocks processed for histology but it is estimated that with selection 5–8 blocks will detect 90–98% of the prostatic carcinomas that are represented in a specimen.

Postoperative necrobiotic granuloma

— post-TURP fibrinoid necrosis with palisading histiocytes. Also granulomatous prostatitis (idiopathic, post BCG).

Postoperative spindle cell nodule and inflammatory myofibroblastic tumour (IMFT)/pseudosarcomatous fibromyxoid tumour

See Chapter 30.

Prognosis

Prognosis in prostatic cancer is related to the volume of tumour, Gleason score and extracapsular extension. Tumour volume can only really be derived by systematic measurement of serial slices of prostatectomy specimens. However, the proportion or percentage of TURP chippings or needle biopsy cores involved gives a reasonable estimate of disease extent. Overall 10-year survival is 50% and up to 30% can be regarded as cured. Gland-confined disease (pT1, pT2) shows 80–95% 10-year survival depending on tumour volume, whereas extraprostatic extension (pT3, pT4) decreases 10-year survival to 60% and gives a "cure" rate of only 25%. Other prognostic factors are positive surgical margins, perineural and lymphovascular invasion and serum PSA levels (an indirect indicator of tumour volume and extension). Treatment (surveillance only for localized disease, radical prostatectomy, radiotherapy, hormonal manipulation) is tailored to the patient's age, general level of health and clinicopathological stage of disease. Non-surgical modalities are of use in localized disease and as palliation in locally advanced or metastatic disease. Indications for radical prostatectomy are a younger patient (up to sixth/seventh decade) with persistent but modestly elevated serum PSA (less than 10–15 ng/ml), needle biopsy-proven adenocarcinoma and an absence of extraprostatic spread on MRI and bone scan. Serum PSA >15 ng/ml is associated with a greater likelihood of the tumour not being gland-confined and subsequent positive surgical margins. Gleason score $\geq 4 + 3 = 7$, extracapsular disease or positive surgical margins necessitate postoperative radiotherapy as they are predictors of poor prognosis and potential treatment failure.

Serum PSA level

High levels (>4–5 ng/ml at ≥50 years; >2.8 ng/ml at <50 years; free to total ratio <15%) of PSA should prompt processing of further tissue and/or multiple levels as there is a strong correlation with the presence of adenocarcinoma (elevated in 64% of cases). Levels above 4 ng/ml and 10 ng/ml confer cancer risks of 25% and 60%, respectively. There is also a significant positive correlation with Gleason grade as poorly differentiated tumours are usually of high volume. Serum levels >0.2 ng/ml post radical prostatectomy can represent biochemical relapse, local recurrence or metastatic disease. Elevated levels in inflammatory conditions (prostatitis, infarct) are usually of lesser magnitude, transitory and resolve with time and treatment. Screening is based on digital rectal examination, transrectal ultrasonography and serum PSA levels. Tissue

expression of PSA/PSAP is useful in identifying a prostatic origin for metastatic carcinoma and distinguishing it from poorly differentiated TCC (PSA/PSAP negative, CK7/CK20/34βE12/p53 positive), particularly in TURP specimens derived from the bladder neck or, rarely, in prostatic needle biopsies.

Immunophenotype

The vast majority of prostatic adenocarcinomas are strongly PSA and PSAP positive, although a small minority of poorly differentiated tumours may show only focal staining for monoclonal PSA. This is strengthened by use of polyclonal PSA with PSAP, the caveat being the cross-reaction of rectal carcinoid and anal tumours with the latter. Loss of the basal layer and lack of 34βE12 has become a standard tool in diagnosing prostatic adenocarcinoma. This can be equally well demonstrated with other basal layer markers such as CK5/6 or p63. AMACR/P504S has emerged as a good diagnostic counterpart to 34βE12, showing cytoplasmic granular positivity in up to 80% of malignant prostatic glands or atypical glands suspicious of malignancy. It arose as a product of high throughput microarray technology and although it has sensitivity and specificity limitations, it is now routinely used in tandem with 34βE12 in the assessment of atypical glandular foci. Note that it can also be positive in PIN, atypical adenomatous hyperplasia, nephrogenic adenoma and prostatic periurethral ducts, emphasizing the importance of using both markers allied to morphology. The role of negative CK7/CK20/p53/34βE12 staining in prostatic carcinoma vs. urothelial cancer has already been mentioned.

9. OTHER MALIGNANCY

Lymphoma/leukaemia

— especially chronic lymphocytic leukaemia (20% of cases at autopsy).
— primary MALToma (rare) or secondary to systemic/nodal lymphoma; prognosis is poor.

Leiomyosarcoma

— adults; 26% of prostatic sarcomas, local recurrence and metastases common.

Other rare sarcomas must be distinguished from sarcomatoid carcinoma with homologous or heterologous differentiation.

Embryonal rhabdomyosarcoma

— <20 years age.
— second commonest site after head and neck.
— usually extensive tumour of prostate, bladder and surrounding soft tissues with a botryoid (grape-like) appearance.
— cellular subepithelial cambium layer, loose myxoid zone, cellular deep zone ± rhabdomyoblasts.
— vimentin, desmin, myo D1, myogenin positive. A minority are alveolar and more aggressive.

32
Urethral Carcinoma

1. GROSS DESCRIPTION

Specimen

— biopsy/urethrectomy or as part of cysto(prostato)urethrectomy.
— weight (g) and size/length (cm), number of fragments.
— urethral cancers can present with haematuria, urinary hesitancy or retention. Proximal lesions present at a late stage. Investigation is by urethroscopy and biopsy, often combined with cytoscopy, and CT/MRI scan to determine tumour stage. Treatment is by surgical excision, the extent of which depends on the location and stage of disease, e.g. local excision for cancer of the distal or meatal urethra. Radiotherapy can preserve the penis but results in troublesome stricturing. Advanced proximal tumours may require a combination of radical surgery and radiotherapy for palliative control. Brachytherapy and radiosensitizing chemotherapy are other options. Secondary urethral cancers from the penis or bladder are excised as part of a penectomy (see Chapter 34) or cysto(prostato)urethrectomy, respectively. In women, urethrectomy is usually in continuity as part of a radical cystectomy. In men, preoperative biopsies are carried out to determine the presence of urethral disease (either in-situ or invasive) and the procedure carried out in two stages, viz cystoprostatectomy down to the level of the urogenital diaphragm and then a perineal urethrectomy for the residual urethra.

Tumour

Site

— prostatic/bulbomembranous/pendulous urethras/meatus.

Size

— length × width × depth (cm) or maximum dimension (cm).

Appearance

— polypoid/verrucous/papillary/sessile/ulcerated/ pigmented.

Edge

— circumscribed/irregular.

2. HISTOLOGICAL TYPE

Primary urethral carcinoma is rare and a urethral cancer is much more likely to represent secondary involvement from adjacent structures, e.g. penis or urinary bladder.

Squamous cell carcinoma

— 60–70% of cases.
— distal.
— keratinizing/non-keratinizing.
— large cell/small cell.
— verrucous: exophytic, pushing deep margin of cytologically bland bulbous processes. May coexist with usual squamous carcinoma.

Transitional cell carcinoma

— 20–30% of cases.
— proximal.

Adenocarcinoma

— 10% of cases.
— female > male; arising in strictures, diverticula or fistulae.
— glandular, enteric, mucinous, signet ring cell, papillary, hob-nail or clear cell patterns with or without urethritis cystica/glandularis.
— prostatic urethra: mesonephroid/endometrioid carcinoma (PSA positive), also known as carcinoma of the prostatic periurethral ducts. See Chapter 31.

Adenosquamous carcinoma

— rare.

Small cell carcinoma

— primary or secondary from lung.
— CAM5.2/synaptophysin/CD56 positive.

Malignant melanoma

— 4% of urethral malignancy.
— extensive radial growth is usual, leading to local recurrence. Spread is common to regional nodes, liver, lungs and brain. Prognosis, which is poor, relates to the tumour thickness. Mucosal junctional activity indicates a primary lesion.

Metastatic carcinoma

— multifocal/direct spread: urothelial cancer from bladder is commoner than a primary lesion. Other cancers that spread directly are penis, rectum, vagina, cervix and endometrium.
— distant spread: ovary, kidney (distinguish from primary clear cell carcinoma).

3. DIFFERENTIATION/GRADE

Well/moderate/poor/undifferentiated, or Grade 1/2/3/4.

— for squamous cell carcinoma based on cellular atypia, keratinization and intercellular bridges, and, for adenocarcinoma on the tumour percentage gland formation (well/G1: >95%; moderate/G2: 50–95%; poor/G3: <50%).

WHO I/II/III for transitional cell carcinoma (see Chapter 30).

4. EXTENT OF LOCAL TUMOUR SPREAD

Border: pushing/infiltrative.
Lymphocytic reaction: prominent/sparse.
The TNM classification applies to carcinomas of the urethra and transitional cell carcinoma of the prostate and prostatic urethra.

Urethra (male and female)

pTa non-invasive papillary, polypoid or verrucous carcinoma
pTis carcinoma in situ
pT1 tumour invades subepithelial connective tissue
pT2 tumour invades any of: corpus spongiosum, prostate, periurethral muscle
pT3 tumour invades any of: corpus cavernosum, beyond prostatic capsule, anterior vagina, bladder neck
pT4 tumour invades other adjacent organs.

Transitional cell carcinoma of prostatic urethra

pTis pu: carcinoma in situ, involvement of prostatic urethra
pTis pd: carcinoma in situ, involvement of prostatic ducts
pT1 tumour invades subepithelial connective tissue
pT2 tumour invades any of: prostatic stroma, corpus spongiosum, periurethral muscle
pT3 tumour invades any of: corpus cavernosum, beyond prostatic capsule, bladder neck (extraprostatic extension)
pT4 tumour invades other adjacent organs (invasion of the bladder).

Distinction must be made between periurethral duct involvement by tumour (pTis pd) and invasion into periurethral or prostatic stroma as the latter worsens the prognosis.

In urethral diverticular carcinoma, a distinction between T2 and T3 is not possible and it is classified as T2.

5. LYMPHOVASCULAR INVASION

Present/absent.
Intra-/extratumoral.

6. LYMPH NODES

Site/number/size/number involved/limit node/extracapsular spread.
Regional nodes: inguinal, pelvic.

pN0 no regional lymph node metastasis
pN1 metastasis in a single regional lymph node ≤2 cm maximum dimension

pN2 metastasis in a single regional lymph node >2 cm maximum dimension or multiple regional lymph nodes.

7. EXCISION MARGINS

Distances (mm) to the proximal and distal longitudinal and deep circumferential resection limits.

8. OTHER PATHOLOGY

Urethral involvement by bladder carcinoma is much commoner than primary urethral carcinoma, which is a relatively rare disease. In the female the urethra is short (4 cm) and removed by cystectomy, which involves total urethrectomy, but there is potential for local recurrence in the residual male urethra. The histological status of the prostatic urethra is therefore assessed by biopsy prior to definitive surgical resection and consideration of cytoprostatourethrectomy.

Multifocal transitional cell carcinoma of urethra, bladder, ureter, renal pelvis can occur either as papillary carcinoma, carcinoma in situ or Pagetoid urethral spread from a bladder lesion.

Female:male ratio 3:1 for urethral carcinoma.

Carcinomas arising proximally (proximal third in women; prostatic, bulbomembranous urethra in men) are generally transitional cell carcinoma, while distal lesions (distal two-thirds in women; penile urethra in men) are usually squamous cell carcinoma. In the distal third they are often well-differentiated squamous cell or verrucous in type.

Clear cell (mesonephroid) adenocarcinoma is rare, arising in either the female or prostatic urethra where it may be associated with a stricture or diverticulum. It should be distinguished from similar lesions arising in the female genital tract and metastatic renal cell adenocarcinoma by clinical history and anatomical distribution of disease. Another differential diagnosis is nephrogenic adenoma, which is usually small and lacks significant cellular atypia and mitoses. Endometrioid carcinoma arises from periurethral prostatic ducts (PSA, PSAP positive) and may be oestrogen sensitive.

Nephrogenic adenoma is a reactive (probably metaplastic) proliferative lesion that does not predispose to but rarely may be associated with concurrent carcinoma, e.g. with adenocarcinoma in a urethral diverticulum. It usually has an exophytic, polypoid or papillary growth pattern with a tubular proliferation of cuboidal epithelium in the underlying lamina propria. Other protuberant urethral lesions than can mimic carcinoma at cystoscopy are benign prostatic urethral polyp, prominent veru montanum, fibrovascular polyp, villous adenoma and inverted transitional cell papilloma. Condyloma accuminatum associated with "high-risk" HPV types (16, 18, 31, 33, 35) may undergo malignant transformation to verrucous or infiltrating squamous cell carcinoma.

Prognosis

Distal urethral carcinoma (well-differentiated squamous/verrucous) presents early with a reasonable prognosis. Overall prognosis of urethral

carcinoma (40% 5-year survival) relates to the anatomical site and stage of disease, e.g. pendulous urethral carcinomas have 5-year survivals of 60–70% while the figure for bulbomembranous/prostatic lesions is 20%. Proximal cancers also present at a more advanced stage and with high-grade (poorly differentiated) histology in which it may be difficult to distinguish squamous from transitional cell carcinoma.

9. OTHER MALIGNANCY

Lymphoma/leukaemia
— as a manifestation of systemic disease.

Embryonal rhabdomyosarcoma
— sarcoma botryoides in children.
— superficial subepithelial cambium layer, intermediate myxoid zone, deep cellular zone, desmin/myo D1/myogenin positive.

Aggressive angiomyxoma
— myxoid stroma/thick vessels.
— locally recurrent/infiltrative.

33
Testicular Cancer

1. GROSS DESCRIPTION

Specimen

— biopsy (open or needle)/radical orchidectomy (testis, tunica vaginalis, coverings and spermatic cord).
— weight (g) and size (cm)–overall and testicular.
— length of spermatic cord (cm).

Tumour

Site

— testicular/paratesticular.
— bilateral: 1–3% of cases, synchronous or metachronous, similar or dissimilar types. Commonest is seminoma or spermatocytic seminoma but beware lymphoma in the older age group.
— testicular cancer usually presents with a painless lump or swelling of some duration. Investigation involves careful clinical examination and ultrasound assessment to detect hypoechoic areas of tumour. Tumour staging is by chest X-ray for pulmonary involvement and CT scan for abdominopelvic and mediastinal lymph node disease. FNA and needle biopsy are avoided due to the potential risk of iatrogenic tumour dissemination and because a testis should always be excised if there is a suspicion of tumour. Exceptions to this would be medically unfit patients or those with known disseminated leukaemia, lymphoma or carcinoma in whom FNA/core biopsy would provide a relatively accessible and non-invasive tissue diagnosis of relapse as a basis for further treatment. In the orchidectomy specimen the pathologist must determine: a. the extent of the tumour spread, b. distinguish between seminoma (radiosensitive), teratoma (chemosensitive) and sex cord stromal tumours, and c. establish if blood or lymphatic vascular invasion is present (indicator for chemotherapy in stage I disease). Serum AFP and HCG are significantly raised in non-seminomatous germ cell tumour while HCG may be modestly elevated in pure seminoma, and LDH is an indicator of bulky advanced or metastatic disease. Resection is by radical inguinal orchidectomy as a scrotal approach would then in addition incorporate pelvic lymph nodes as regional.

Size
— length × width × depth (cm) or maximum dimension (cm).

Appearance
— pale/fleshy/nodular ± necrosis: seminoma/lymphoma.
— cysts/cartilage ± necrosis: teratoma.
— haemorrhage: choriocarcinoma, yolk sac tumour.
— fibrous/calcific scar: regression.
— pale or tan/lobulated, often small and circumscribed: Leydig cell/stromal tumour.
— note that some inflammatory conditions, e.g. granulomatous orchitis or malakoplakia, can mimic germ cell tumour macroscopically.

Edge
— circumscribed/irregular.

2. HISTOLOGICAL TYPE
Therapeutic distinction is drawn between seminomatous and non-seminomatous germ cell tumours due to adjunctive radiotherapeutic and chemotherapy approaches, respectively.
NB: List and semiquantify the percentage of tumour types present in a mixed germ cell tumour. Histopathological grading is not applicable.
Germ cell tumours comprise 95% of testicular neoplasms (of which 40–50% are seminoma) and sex cord stromal lesions 4%.

Seminoma
— classical (93% of cases) or anaplastic with the same behaviour despite different mitotic rates and the term anaplastic is not really justified.
— typically large, polygonal cells with clear to eosinophilic cytoplasm and an intervening stroma with aggregates of lymphocytes. Granulomas and HCG positive syncytiotrophoblastic giant cells may also be present.
— usually sheets of cells but trabecular, diffuse single cell interstitial, pseudoglandular and tubular patterns also occur, and "cystic" spaces due to oedema. Sometimes sclerotic stroma.
— spermatocytic: benign with three cell types and PLAP negative in old age (see page 353).

Malignant teratoma

— differentiated, MTD.	Embryonic differentiation
— intermediate (a mix of MTD and MTU), MTI.	
— undifferentiated (syn. embryonal carcinoma), MTU.	
— yolk sac (endodermal sinus) tumour, YST.	Extraembryonic differentiation
— trophoblastic/choriocarcinoma, MTT*.	

*Requires additional specific chemotherapy.

Teratoma differentiated (5–10% of cases) may have:

— *mature tissues*: benign in childhood (usually <4 years of age) but potentially malignant in the postpubertal patient. Somatic tissues commonly represented are: cartilage, muscle, neuroglia, enteric glands, squamous/respiratory and urothelial epithelia. Ovarian type cystic teratoma with sebum and hair is rare. Distinguish also from a benign testicular epidermoid cyst containing laminated keratin and lined by mature stratified squamous epithelium but no mural appendage structures or adjacent ITGCN.
— *immature tissues*: e.g. cartilage, variably cellular mesenchymal stroma arranged concentrically around glandular epithelium, neuroectoderm, blastema and embryonic tubules. It is uncertain as to whether grading is of prognostic significance but a semi-quantitative and qualitative assessment of the amount (rare, focal, diffuse) and degree of immaturity (low/high-grade) should be made.
— *malignant transformation*: adenocarcinoma, squamous carcinoma, but more than 50% are sarcoma of no specific type, or showing distinct differentiation features, e.g. leiomyosarcoma, rhabdomyosarcoma, PNET (a designation of sarcoma requires at least one low-power field of atypical mesenchyme).

Mixed germ cell tumour

More than one germ cell type in any combination occurs in 30–50% of cases, e.g. seminoma and embryonal carcinoma, embryonal carcinoma and teratoma. Sample extensively (1 block/cm tumour diameter and target block any unusual gross appearance, e.g. the association of choriocarcinoma with haemorrhage) to allow for this tumour heterogeneity, particularly if there are significantly elevated serum AFP and HCG levels.

Anaplastic germ cell tumour

— morphologically and immunohistochemically intermediate between seminoma and embryonal carcinoma.

Mixed germ cell and sex cord stromal tumour

— gonadoblastoma: mixture of seminoma type cells and sex cord cells usually progressing to invasive germ cell tumour, mostly seminoma.

Sex cord stromal tumours

— Leydig: 1–3% of testicular neoplasms and 30% hormonally active with gynaecomastia. Well circumscribed with eosinophilic or clear cells and Reinke's crystalloids (40%). Alpha-inhibin, melan-A positive, cytokeratin ±, AFP/PLAP negative.
— Sertoli: not otherwise specified (including sclerosing variant) and large cell calcifying types. Sheets, nests, tubules and cords of Sertoli cells with a hyaline stroma. Cytokeratin, alpha-inhibin positive/PLAP negative. Often non-functional.
— granulosa: adult—microfollicular (Call-Exner bodies), nuclear grooves with a range of morphology similar to that seen in the ovary. Rare,

usually non-functional and 10% malignant. Cytokeratin ±, alpha-inhibin and melan-A positive.
juvenile—<1 year old, cystic follicular structures, benign. The commonest neonatal testicular cancer.
— undifferentiated or mixed types.

Malignancy (10% of sex cord stromal tumours) relates to size (>5–7 cm), cellular atypia, mitoses (>3/10 hpfs), infiltrative margins, vascular invasion and a high Ki-67 proliferation index.

A diagnostic pitfall is sex cord stromal tumour positivity for S100 and melan-A mimicking metastatic melanoma.

Other tumours

— adenocarcinoma of the rete (rare, poor prognosis).
— cystadenocarcinoma of the epididymis (very rare). Papillary cystadenoma is associated with von Hippel-Lindau syndrome.
— lymphoma.

Diffuse large B-cell non-Hodgkin's in old age and uni-/bilateral, comprising 5% of testicular neoplasms. Primary (60% of cases) or secondary to systemic/nodal disease and often associated with disease elsewhere, e.g. CNS, skin, soft tissues, liver, kidney, lung, bone, orbit and Waldeyer's ring. Classically shows an interstitial/peritubular pattern of infiltration. Prognosis is stage dependent:

stage I 60% 5-year survival (>stage I 17%).
children: Burkitt's lymphoma ("starry sky" pattern, CD10/Ki-67 positive).
— leukaemia:
ALL: children, site of relapse in 5–10% and predictive of systemic relapse
CLL: 20–35% of patients involved.

Leukaemia can be bilateral and the presenting feature in a minority of cases.

Plasmacytoma: rare, usually secondary to an established myeloma. Differential diagnosis is spermatocytic seminoma. Plasmacytoma expresses CD79a and CD138.

— metastatic carcinoma:

Prostate, lung, malignant melanoma, colon, kidney, stomach, pancreas. Bilaterality, vascular involvement and absence of intratubular germ cell neoplasia (ITGCN) favour metastatic disease.

— carcinoid tumour:

Good prognosis, a monodermal teratoma but 20% have other teratomatous elements. Exclude metastatic carcinoid (vascular invasion, extratesticular extension, bilateral).

— primitive neuroectodermal tumour:

Can be primary but more frequently arises within a testicular teratoma.

Paratesticular: lipo-, rhabdo-, leiomyosarcoma, mesothelioma of the tunica vaginalis, lymphoma (secondary from testis)

— liposarcoma: adults and well-differentiated adipocytic/sclerotic with variation in adipocyte size and scattered lipoblasts. Local excision and 23% local recurrence. Occasionally an extension from a retroperitoneal neoplasm.
— rhabdomyosarcoma: in children of embryonal round cell (± spindle cells) type with mitoses and necrosis. Desmin and myogenin/myo D1 positive. Excision and adjuvant therapy give 80% long-term survival. There is also a low-grade fascicular spindle cell variant of good prognosis but alveolar rhabdomyosarcoma with adverse outlook.
— leiomyosarcoma: adults with atypia, necrosis, mitoses.
— mesothelioma: cystic/solid/nodular masses lining a hydrocoele/hernia sac and a variably aggressive clinical course. There may be associated asbestos exposure.
— desmoplastic small round cell tumour: lower abdomen and pelvi-inguinal area of young men. Nests of small cells in a fibrous stroma. Polyimmunotypic—cytokeratin, desmin, synaptophysin, WT1 positive.

3. EXTENT OF LOCAL TUMOUR SPREAD

Border: pushing/infiltrative.

Lymphocytic reaction: prominent/sparse.

Lymphocytic reaction is a consistent (80%) feature of seminoma, and granulomas can also be present in up to 50% of cases. Sometimes the inflammatory infiltrate can be so intense that it partially obscures the germ cells and immunohistochemical markers are necessary. The intensity of inflammation and presence of granulomas are not prognostically significant.

ITGCN/carcinoma in situ: sample the adjacent testis.

Intratubular spread: seminoma/embryonal carcinoma.

It can be difficult to distinguish between ITGCN and intratubular spread, although in embryonal carcinoma ITGCN will be PLAP/CD117 positive and intratubular spread PLAP negative/CD30 positive. Intratubular embryonal carcinoma has been suggested as an intermediate step between ITGCN and established embryonal carcinoma. Intratubular spread of seminoma and ITGCN into the rete can also mimic embryonal carcinoma or carcinoma of the rete.

Rete: Pagetoid or luminal spread—seminoma/embryonal carcinoma. Extratesticular extension of germ cell tumours is commoner at the rete/hilum.

Tunica albuginea/vaginalis, epididymis, spermatic cord.

The TNM classification applies to germ cell tumours of the testis.

pTis	ITGCN (carcinoma in situ)
pT1	tumour involves testis and epididymis or tunica albuginea, no lymphovascular invasion or involvement of tunica vaginalis
pT2	tumour involves testis and epididymis with lymphovascular invasion, or extends through tunica albuginea to involve tunica vaginalis

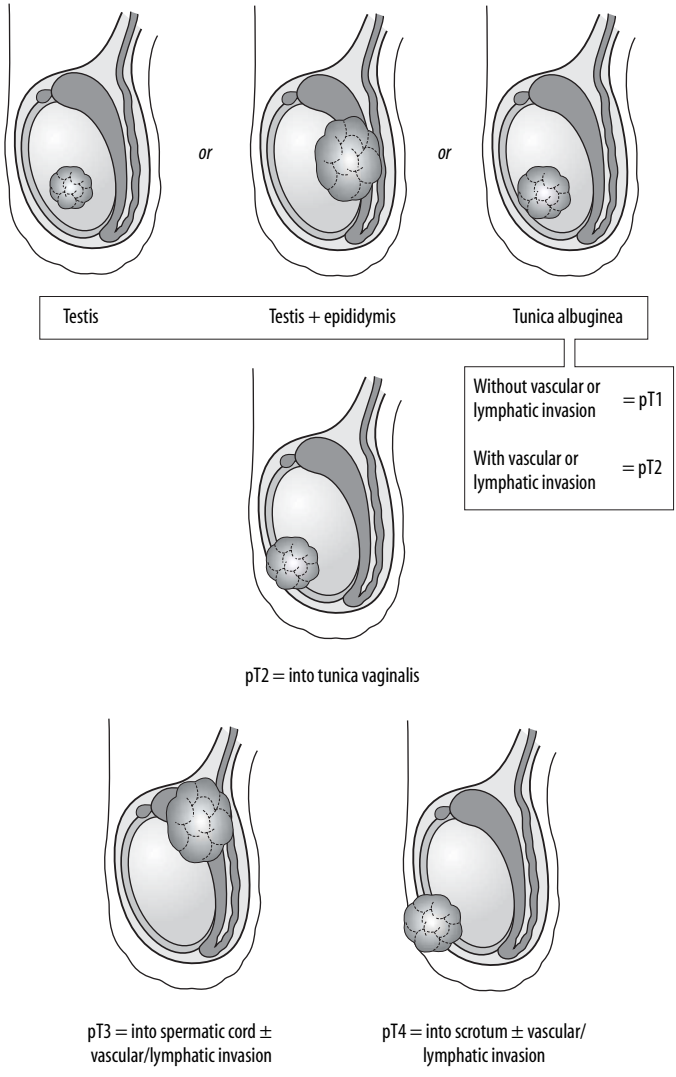


FIGURE 33.1. Testicular germ cell tumours.

pT3 tumour involves spermatic cord ± lymphovascular invasion
pT4 tumour involves scrotum ± lymphovascular invasion.

In mixed germ cell tumours the pT classification is determined by the highest stage of its components. Synchronous bilateral tumours are staged as independent primary tumours.

Invasion beyond tunica albuginea involves scrotal structures except scrotal skin or subcutaneous tissues (both pT4).

Invasion of the spermatic cord refers to direct extension beyond the rete or epididymis.

4. LYMPHOVASCULAR INVASION

Present/absent.
Intra-/extratumoral.

Lymphovascular invasion is correlated with a significantly elevated risk of distant metastasis and is an indication for chemotherapy. Consequently, strict criteria for its identification are necessary, i.e. an endothelial lined space with tumour conformed to its shape ± thrombosis or a point of attachment to the endothelium. Sample particularly the tumour/parenchyma interface and the overlying tunica looking for vasculocentric nodular deposits.

5. LYMPH NODES

Site/number/size/number involved/limit node/extracapsular spread.
Regional nodes: abdominal periaortic and pericaval, those located along the spermatic veins. The intrapelvic and inguinal nodes are considered regional after scrotal or inguinal surgery.

pN0 no regional lymph node metastasis
pN1 regional lymph node metastasis ≤2 cm and ≤5 positive nodes
pN2 regional lymph node metastasis >2 cm but ≤5 cm, or >5 positive nodes, or extranodal extension
pN3 regional lymph node metastasis >5 cm.

Seminoma tends to metastasize through lymphatics while choriocarcinoma shows haematogenous spread with presentation from metastatic disease to lung, liver, brain, bone and gut. Embryonal carcinoma spreads by a combination of these mechanisms. Nodal involvement depends on the stage of disease and laterality of the primary tumour. Initial spread is periaortic but external iliac and inguinal node involvement may be seen if the tumour spreads to the epididymis and scrotal skin, respectively. Mediastinal and left supraclavicular node metastases occur late in the disease course.

6. CLINICAL STAGE

Modified Royal Marsden Staging System

I tumour confined to the testis
II nodes involved below the diaphragm

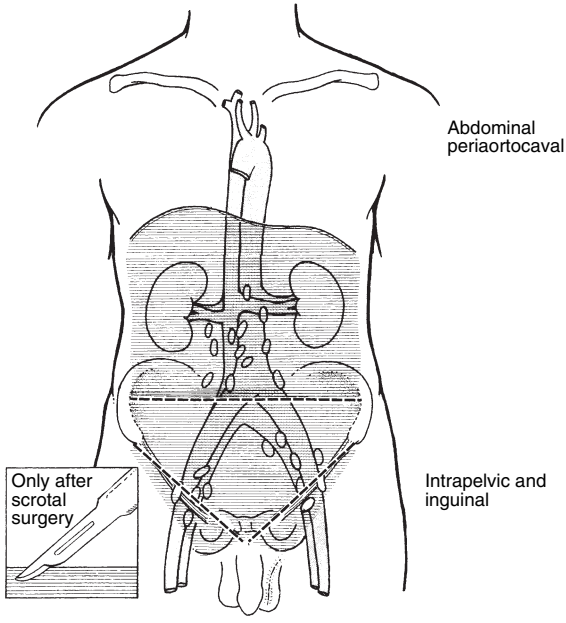


FIGURE 33.2. Testicular germ cell tumours: regional lymph nodes.

III nodes involved above the diaphragm—supraclavicular or mediastinal
IV extranodal metastases—lung or brain.

Up to 30% of patients with seminoma have metastases at the time of diagnosis, 50–60% with embryonal carcinoma and the majority with choriocarcinoma.

Clinical staging is based on the determination of the anatomical extent of disease and the assessment of postorchidectomy serum markers LDH, human chorionic gonadotrophin β subunit (HCG) and AFP. High levels (AFP >10 000 ng/ml, HCG >50 000 IU/l, LDH >10× normal) indicate worse prognosis and usually a diagnosis of non-seminomatous germ cell tumour.

Metastatic germ cell tumour is an important diagnostic consideration in a young male with evidence of extensive visceral disease but no known primary somatic site carcinoma. This is particularly so if there is cervical, mediastinal or retroperitoneal lymphadenopathy or lung metastases. Ultrasound may show a small or scarred testicular lesion. Biopsy of metastases may only show undifferentiated tumour and chemotherapy is instigated empirically on the basis of elevated serum markers. Occasionally poorly differentiated carcinoma of stomach, lung or bladder may

cause a modest elevation in serum HCG. Crucially, the pathologist has to think of the possibility of germ cell tumour and look for the distinctive morphological and immunohistological clues (PLAP, CD30, OCT 3/4).

7. EXCISION MARGINS

Distances (mm) to the parietal tunica margin and proximal limit of the spermatic cord.

8. OTHER PATHOLOGY

ITGCN is the precursor lesion of all germ cell tumours except spermatocytic seminoma, infantile teratoma differentiated and yolk sac tumours. It is usually seen in a patchy distribution within the testicular tubules away from and adjacent to the tumour in up to 80% of seminomas and malignant teratoma. It may also be detected by needle biopsy as a risk factor for tumour development in the contralateral testis, particularly if the testis is soft, atrophic or of low volume. It can be treated by low-dose irradiation as 50–90% of untreated ITGCN will progress to germ cell tumour over a 5-year period. Chemotherapeutic agents do not cross the blood/testis barrier. It comprises a proliferation of seminoma-like cells (clear cytoplasm, PAS/PLAP/CD117 (c-kit)/p53/OCT 3/4 positive) at the base of the tubules, which often have a hyalinized and thickened basement membrane and absence of spermatogenesis. It can be associated with intratubular or extratubular (microinvasive) interstitial extension as either seminoma or embryonal carcinoma and usually accompanied by a herald lymphocytic infiltrate.

Prior testicular tumour on the contralateral side confers an increased malignancy risk ×5–10.

Maldescent/cryptorchidism and infertility confer an increased malignancy risk ×3–5 and 1% incidence, respectively.

"Scar" cancer (fibrosis, haemosiderin-laden macrophages, intratubular calcification) with retroperitoneal secondaries is regression of the primary and presentation with metastatic disease, especially embryonal carcinoma or choriocarcinoma.

Age is also a helpful indicator in that malignant germ cell tumours and sex cord stromal tumours present in the third and fourth decades but lymphoma and spermatocytic seminoma occur in old age. Seminoma is usually in patients 10 years older than those with non-seminomatous germ cell tumours. Yolk sac tumour is the commonest testicular neoplasm in children but also a common component of adult germ cell tumours.

Other scrotal swellings mimicking testicular cancer are: epididymo-orchitis, granulomatous orchitis, malakoplakia and peritesticular hydrocoele. Ultrasound examination is useful in delineating the latter and intratesticular lesions. This, coupled with increased male health awareness, has led to an increasing proportion of small and unusual tumours being detected, e.g. sex cord stromal lesions, epidermoid inclusion cyst.

FNAC can be of use in those patients suspected of having metastatic carcinoma in the testes or testicular relapse in lymphoma and leukaemia. It is usually limited in germ cell tumours to those patients who are

medically unfit for orchidectomy but in whom a tissue diagnosis is necessary for further management. Due to the considerable heterogeneity of germ cell tumours, it can be subject to marked sampling error. Abdominal and thoracic aspiration cytology (± core biopsy) are useful for the assessment of germ cell tumour metastases which should be categorized as seminomatous (requiring radiotherapy ± chemotherapy depending on the bulk of disease) or non-seminomatous. The latter is either pure teratomatous (requiring surgery) or other, e.g. embryonal carcinoma or yolk sac tumour (requiring chemotherapy). Serum HCG and AFP levels are also useful in making these management decisions.

Spermatocytic seminoma (1–2% of germ cell tumours) has indolent behaviour and is treated by orchidectomy alone. It presents in the older age group (50–70 years) and shows no evidence of adjacent ITGCN. It is lobulated ± microcystic with stromal oedema and comprises a tripartite population of small, intermediate and large glycogen negative cells with indistinct cell boundaries, a "spireme" chromatin pattern and scattered mitoses. It lacks a stromal lymphocytic component, is PLAP/HCG/EMA/CD30 negative and variably CAM5.2 positive. Differential diagnosis is seminoma of usual type (distinct cell boundaries, uniform polygonal cells with clear cytoplasm, an enlarged nucleus with nucleoli and clumped nuclear chromatin, lymphocytic stroma, PLAP/CD117/OCT 3/4 positive) and malignant lymphoma (CD45, CD20, κ/λ light chain restriction, interstitial/peritubular infiltration, can be bilateral). Rarely it undergoes highly malignant (rhabdomyo-)sarcomatous change.

Anaplastic germ cell tumour at low power is seminoma-like but at high power there is cellular atypia/anaplasia/mitoses. Variable PLAP/CAM5.2 positivity.

Embryonal carcinoma (MTU) is present in 87% of non-seminomatous germ cell tumours but usually as part of a mixed germ cell tumour. It comprises primitive anaplastic epithelial cells in solid, glandular or tubulopapillary patterns.

Yolk sac tumour is the commonest prepubertal testicular germ cell tumour and is present in up to 40–50% of adult lesions. It is histologically heterogeneous assuming a spectrum of patterns, the commonest being microcystic (honeycomb, reticular, vacuolated), papillary, endodermal sinus (perivascular Duvall-Schiller bodies), solid, myxomatous and glandular (enteric or endometrioid). Other characteristics are PAS positive diastase-resistant, intra- and extracellular hyaline globules and deposition of extracellular basement membrane. AFP is present in the vast majority of cases but can be patchy in expression and is expressed in the tumour cell cytoplasm rather than the globules.

Note that there are terminological differences between the British Testicular Tumour Panel (BTTP) and the WHO systems interpreted as follows (optional):

BTTP	WHO
Malignant teratoma differentiated, MTD	Teratoma mature

MTD (with immature elements)	Teratoma immature
MTD (with malignant transformation)	Teratoma with an overtly malignant somatic component
Malignant teratoma intermediate, MTI	Embryonal carcinoma or yolk sac tumour mixed with mature or immature teratoma ("terato-carcinoma")
Malignant teratoma trophoblastic, MTT	Choriocarcinoma
Malignant teratoma undifferentiated, MTU	Embryonal carcinoma.

The BTTP classification is based on the presumption that all testicular teratomas arise from pluripotential stem cells and show variable type and differentiation rather than representing distinct entities. However, there is also justification in the latter approach because of their distinctive morphological features, correlation with serum tumour markers and prognostic associations, e.g. yolk sac and embryonal carcinoma.

Immunophenotype

The reactions of different tumour types with immunohistochemical markers are given in Table 33.1 and summarized below.

CIS/ITGCN	PLAP+	CAM±	OCT 3/4+	CD117+
Seminoma	PLAP+	CAM–	OCT 3/4+	CD117+
YST	AFP+	CAM+		
MTU	PLAP±	CAM+	OCT 3/4+	CD30+
MTT	HCG+	CAM±		

PLAP positivity in seminoma/ITGCN is membranous and not cytoplasmic as seen in some non-small cell lung carcinomas and malignant melanomas. OCT 3/4 is a nuclear epitope. Markers may also help distinguish metastatic embryonal carcinoma (CAM+, PLAP±, CD30±, EMA–) from metastatic carcinoma (CAM+, PLAP–, CD30–, EMA+). Seminoma is generally CAM5.2–, CD30– and EMA– but can show focal positivity for these markers as well as CK7 and AE1/AE3. Embryonal carcinoma is strongly positive for various cytokeratin markers and OCT 3/4 but variable for CD117.

Serum markers often do not show good correlation with their tumour tissue expression but are good for monitoring disease treatment response

Table 33.1

	PLAP	CAM 5.2	AFP	HCG
CIS/ITGCN	+	±	–	–
Seminoma	+	–	±	±
Spermatocytic seminoma	–	–	–	–
YST	±	+	+	±
MTU	±	+	±	±
MTT	±	±	–	+

and relapse as they are raised in 70–75% of patients with non-seminomatous germ cell tumours. Seminoma may have mildly elevated HCG levels (15%) and increased serum PLAP levels (40% of cases). Seminoma and MTD rarely give elevated AFP levels. If present, other elements, e.g. yolk sac tumour or embryonal carcinoma, are identified.

Apparently aberrant tissue expression is acceptable without changing the diagnosis or prognosis, e.g. seminoma with HCG positive syncytiotrophoblastic cells (10–20% of cases) or embryonal carcinoma with elevated serum HCG. MTT (5% of cases) requires biphasic syncytio- and cytotrophoblastic differentiation for diagnosis (although the "syncytio" element may be inconspicuous) and angioinvasion with tumour haemorrhage is common. Designation is dependent on the morphology and not the serum hormone levels. The syncytiotrophoblast is HCG positive capping the cytokeratin 7 positive cytotrophoblast and may also show positive staining for HPL, EMA, cytokeratins, inhibin, PLAP and CEA.

Prognosis

With modern oncological treatment regimes the prognosis of even metastatic germ cell tumour is excellent with more than 90% cure. It relates to serum marker levels, stage of disease, histological type and lymphovascular invasion. Stage I disease and stage II with non-bulky (<5–10 cm) retroperitoneal secondaries have 5-year survival rates of 90–95% for both seminoma and embryonal carcinoma, whereas the rate for bulky stage II tumour is 70–80%. Yolk sac tumour presents as stage I (90%) in childhood with >90% 5-year survivals; however, it can exhibit chemoresistance in adults with metastatic disease. The presence of yolk sac elements in an immature teratoma of childhood is also an indicator for potential recurrence of disease. Extensive pulmonary disease in embryonal carcinoma is a poor prognostic indicator.

Prognosis of seminoma worsens with:

1. Tumour diameter ≥6 cm
2. Age <34 years
3. Vascular invasion.

Prognosis of teratoma worsens with:

1. Increasing stage
2. Presence of MTU
3. Absence of YST
4. Lymphovascular invasion.

The Medical Research Council scheme scores 1 for each of: presence of MTU, absence of YST, lymphatic invasion, blood vessel invasion.

Tumour score:

0–2 surgery with follow-up only
3–4 surgery with adjuvant chemotherapy.

Low volume/percentage tumour area of MTU and low Ki-67 index are beneficial. Relapse rates are 15–20% for seminoma (80% in the retroperi-

toneum) and 30–35% for teratoma (66% in the retroperitoneum, 33% in the lung or mediastinum). Vascular invasion is a strong determinant of postoperative chemotherapy in stage I disease. Stage I and non-bulky stage II seminoma are treated by orchidectomy and radiation to regional node sites—bulky stage II and more advanced disease require more extensive radiotherapy and, in addition, chemotherapy. Non-seminomatous germ cell tumours require orchidectomy and platinum-based chemotherapy supplemented by retroperitoneal lymph node dissection (RPLND) for post-treatment residual disease or recurrent disease refractory to chemotherapy. Postchemotherapy cytoreduction of metastases results in necrosis, xanthomatous inflammation, fibrosis and variably viable tumour tissue. Ominously carcinomatous or sarcomatous (e.g. rhabdomyosarcoma, primitive neuroectodermal tumour) differentiation may occasionally occur. Metastatic disease not infrequently changes differentiation with treatment, leaving residual masses of cystic, mature tissues in the lung or para-aortic nodes which are insensitive to adjuvant therapy, can press on local structures (the growing teratoma syndrome) and may require surgical resection. Alternatively, they can be monitored by serum marker levels and CT scan and further investigated for malignant change if growth recurs. Prognosis of metastatic disease relates to the size, site and number of metastases, the extent of tumour mass shrinkage during chemotherapy, completeness of excision, nature of the resected masses and serum HCG and AFP levels. Metastases comprising total necrosis or fully mature tissue correlate with better prognosis. Fibrosis, necrosis and differentiated teratoma are present in 20–70% of cases; MTU, MTT and YST in 5–25% of cases. A minority of seminomas may develop non-seminomatous germ cell tumour metastases; this may relate either to true transformation of seminoma or a focus of non-seminatous germ cell tumour in the primary lesion which was not sampled. In orchidectomy and RPLND specimens, sufficient numbers of blocks should be sampled to establish the presence of any malignant components as a basis for further chemotherapy, e.g. germ cell, carcinomatous, sarcomatous or primitive neuroectodermal elements. In general, patterns of metastases are:

Primary	Metastasis
Seminoma	Seminoma
MTD	MTI
MTI	MTD, MTI or MTU MTD is usually postchemotherapy maturation
mixed germ cell tumour + MTT	MTT

The number of chemotherapy cycles is minimized by titrating against normalization of the serum marker levels. This is done to decrease the risk of developing a second malignancy in later life, e.g. sarcoma or lymphoma.

34
Penile Carcinoma

1. GROSS DESCRIPTION

Specimen

— wedge biopsy/penile-sparing resection/(glansectomy/partial penectomy)/total penile amputation/radical penectomy (including scrotum, testes, spermatic cords, groin lymph node dissection).
— size (cm) and weight (g).
— penile cancer can present as a warty/nodular lesion, plaque or ulcer commonly on the glans penis or in the coronal sulcus. Investigation is by diagnostic punch or wedge biopsy, although in well-differentiated exophytic lesions definite invasive malignancy may be hard to demonstrate in a limited sample and the clinical impression is then important in designation and planning of management. FNA of inguinal lymphadenopathy may demonstrate metastases as a prequel to radical surgery and regional ilioinguinal lymphadenectomy. Alternatively, nodal enlargement may be solely on the basis of inflammation or infection. CT scan can demonstrate the presence of any ilioinguinal lymphadenopathy that is subclinical in extent. Most penile cancers are superficial and can be treated by limited resection (glansectomy, partial penectomy) with reconstruction of the glans rather than amputation or primary radiotherapy. Accurate assessment of the proximal extent and depth of invasion (e.g. corporal or urethral involvement) by MRI is important to avoid incomplete excision or unnecessarily extensive resection, and in specialist centres this may be determined intraoperatively by frozen section. The treatment goal is complete excision with adequate margins and choice of therapy is related to tumour size, extent of infiltration and destruction of normal tissues. Radiotherapy is reserved for high-stage tumours, recurrences, metastatic disease and patients unfit for surgery. Localized tumours of the prepuce are treated by circumcision. Glansectomy removes the foreskin and glans for carcinoma in situ or localized cancer but there is a higher risk of incomplete removal and local recurrence. Partial penectomy relies on transection of the penis 2 cm proximal to the gross tumour edge but may be precluded in favour of total penectomy because of tumour size, site and destruction. Ilioinguinal lymphadenectomy is for known metastases or negative nodes but poorly differentiated high-risk carcinomas.

Tumour

Site
— urethral meatus/glans/prepuce/coronal sulcus/shaft (dorsal/ventral/lateral).

Size
— length × width × depth (cm) or maximum dimension (cm).
— tumour thickness (mm) is a gauge of depth of invasion and prognosis.

Appearance
— exophytic (warty, verrucous, papillary, fungating).
— superficial spreading (plaque).
— endophytic (sessile, ulcerated, infiltrative).
— pale/pigmented.

Edge
— circumscribed/irregular.

2. HISTOLOGICAL TYPE

Squamous cell carcinoma
— 95% of penile malignancies, 70–80 years of age.
— usual type (70% of cases).
— exophytic or endophytic.
— large cell/small cell.
— keratinizing/non-keratinizing.

variants:

— verrucous: 5–16% of cases and exophytic with a deep pushing margin of cytologically bland bulbous processes. Prone to multifocality and local recurrence if incompletely excised and may dedifferentiate with radiotherapy. Generally a good prognosis. Can coexist with usual squamous carcinoma.
— spindle cell (sarcomatoid): cytokeratin (34βE12) positive spindle cells associated with a surface epithelial origin or more recognizable in-situ or invasive squamous cell component. A high-grade endophytic cancer with poor prognosis.
— basaloid: comprises 5–10% of cases and is a poorly differentiated aggressive high-grade tumour. Usually ulcerated and endophytic with nests of basaloid cells showing abrupt central keratinization or comedonecrosis.
— warty and papillary: exophytic and well differentiated, the former with koilocytic atypia and the latter irregular, complex papillae and stromal cores.
— mixed types: 25% of cases. Adequate tumour sampling is necessary to find less differentiated components.

Basal cell carcinoma
— a local carcinoma of penile skin.

Transitional cell carcinoma
— either as a primary lesion of the proximal urethra or secondary to bladder cancer, both of which can show Pagetoid urethral spread.

Malignant melanoma
— <1% of cases and primary or secondary situated on the glans penis. 50% have nodal metastases at presentation and prognosis is poor, being related to tumour thickness and stage.

Metastatic carcinoma
— rare; prostate, bladder, kidney, gut, testis.
— usually as a late manifestation of systemic disease and can present with priapism or as extramammary Paget's disease from an underlying adnexal tumour or distant spread, e.g. bladder.

3. DIFFERENTIATION
Well/moderate/poor/undifferentiated, or Grade 1/2/3/4.
Many are exophytic and well to moderately differentiated with variable keratinization. Ulcerated, infiltrating cancers of the glans penis tend to be moderately to poorly differentiated. About 50% of shaft cancers are poorly differentiated and only 10% of prepuce tumours. Grading based on the degree of keratinization, intercellular bridges, mitoses, cellular atypia and inflammatory infiltrate correlates with prognosis.

4. EXTENT OF LOCAL TUMOUR SPREAD
Border: pushing/infiltrative.
Lymphocytic reaction: prominent/sparse.
Microscopic growth patterns are verruciform, superficial spreading, vertical with deep penetration or multicentric.

pTis	carcinoma in situ
pTa	non-invasive verrucous carcinoma
pT1	tumour in subepithelial connective tissue
pT2	tumour in corpus spongiosum or cavernosum*
pT3	tumour in urethra or prostate
pT4	tumour in other adjacent structures (scrotum, testis, skin).

Initial spread is local and intercompartmental into the prepuce, coronal sulcus, glans and penile shaft and the depth or extent of this and the pattern of infiltrative spread correlate with the incidence of nodal metastases. Despite the vascularity of the structures, haematogenous spread to the liver, lung and bone is rare (2%).

*Optional descriptors are a. corpus spongiosum and b. corpus cavernosum.

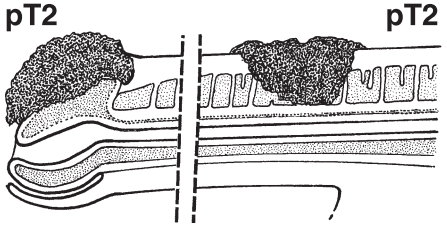


FIGURE 34.1. Penile carcinoma.

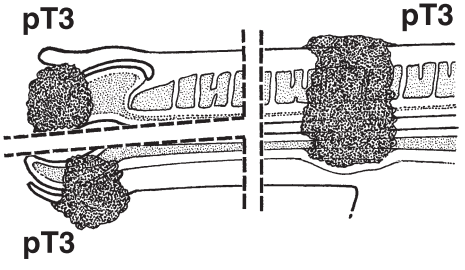


FIGURE 34.2. Penile carcinoma.

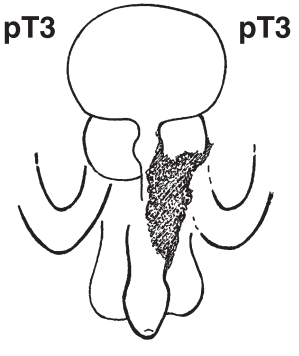


FIGURE 34.3. Penile carcinoma.

5. LYMPHOVASCULAR INVASION

Present/absent.
Intra-/extratumoral.
Vascular invasion is an important adverse factor.

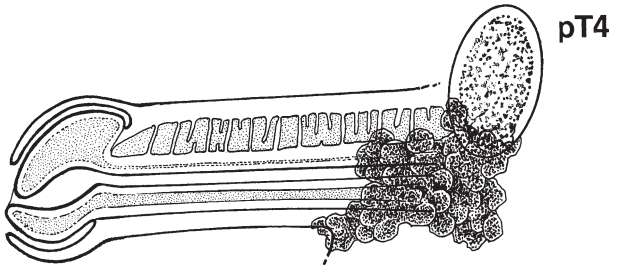


FIGURE 34.4. Penile carcinoma: tumour invades other adjacent structures.

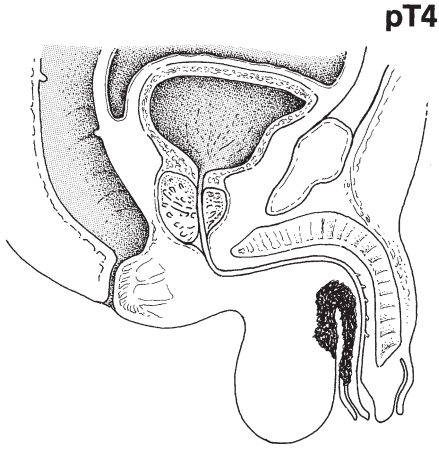


FIGURE 34.5. Penile carcinoma: tumour invades other adjacent structures.

6. LYMPH NODES

Site/number/size/number involved/limit node/extracapsular spread.
Regional nodes: superficial and deep inguinal and pelvic.

pN0 no regional lymph node metastasis
pN1 metastasis in one superficial inguinal lymph node
pN2 metastasis in multiple or bilateral superficial inguinal lymph nodes
pN3 metastasis in deep inguinal or pelvic lymph node(s).

The incidence of nodal metastases is greater (>80%) in deeply invasive than superficially spreading carcinomas (42%). Lymphadenectomy improves prognosis but is carried out only when there are known metas-

tases or in high-grade disease, e.g. basaloid, sarcomatoid or undifferentiated carcinoma. Low-grade tumours such as verrucous carcinoma seldom result in nodal disease, although there may be lymphadenopathy due to inflammation or infection.

7. EXCISION MARGINS

Distance (mm) to the proximal limit of excision in a penectomy specimen.
Distances (mm) to the deep corporal and lateral glans or cutaneous margins in a local resection specimen.
Local recurrence is rare if margins are tumour free.

8. OTHER PATHOLOGY

Balanoposthitis xerotica obliterans
— similar to lichen sclerosus in the vulva, it may be associated with but does not predispose to penile carcinoma.
— present in up to 30–50% of penile cancers, particularly warty and verrucous carcinomas.

Leukoplakia
— hyperkeratosis, epithelial hyperplasia ± dysplasia.

Erythroplasia de Queyrat/Bowen's disease/Bowenoid papulosis
— progression to carcinoma is estimated as 10%/5–10%/0%, respectively. All show features of carcinoma in situ or high-grade penile intraepithelial neoplasia, erythroplasia being a lesion of the glans penis, whereas Bowen's disease and Bowenoid papulosis are abnormalities of the penile/perineal skin. The latter is caused by HPV infection in young men. A minority of Bowen's disease are associated with a visceral malignancy, e.g. lung, gastrointestinal or urinary tract.

Condyloma accuminatum
— HPV 16, 18 are particularly associated with warty and basaloid cancer types.
— other possible predisposing factors for carcinoma are old age (rare <40 years of age), lack of circumcision, poor hygiene and phimosis.

Concurrent urothelial neoplasia ± Pagetoid spread of transitional cell carcinoma into the penile urethra.

Prognosis
More than 95% of penile carcinomas are squamous cell carcinoma. At presentation about 40% are exophytic and superficially invasive with extensive in-situ change, 30% endophytic and deeply invasive, 10–20% verrucous and 5–10% multifocal. Inguinal lymph node metastases are present in 15–30%. Prognosis relates to the tumour site, stage, histological grade and vascular invasion with average 5-year survival rates of 70–80%. Adverse factors are lymphovascular invasion, vertical growth pattern, and basaloid, sarcomatoid, solid, undifferentiated and pseudoglandular subtypes.

9. OTHER MALIGNANCY

Sarcoma

— <5% of penile malignancy especially:

Kaposi's sarcoma: about 20% of AIDS male patients on the skin of the shaft or glans and usually associated with other systemic lesions.

Leiomyosarcoma: 50–70 years of age. Superficial and subcutaneous has a good prognosis whereas corporal in location and deep with early metastases has a poor prognosis.

Epithelioid haemangioendothelioma: varying grade and outlook (CD31/CD34 positive).

Others: angiosarcoma, rhabdomyosarcoma, fibrosarcoma, epithelioid sarcoma.

Lymphoma

— usually secondary to systemic disease.

Lymph Node Cancer

- Nodal Malignant Lymphoma (with comments on extranodal lymphoma and metastatic cancer)

35

Nodal Malignant Lymphoma (with comments on extranodal lymphoma and metastatic cancer)

1. GROSS DESCRIPTION

Specimen

— fine needle aspirate/needle biopsy core/excisional biopsy/regional lymphadenectomy.

Malignant lymphoma presents as persistent, mobile, rubbery and non-tender lymphadenopathy with or without associated systemic symptoms such as weight loss, itch or night sweats. Investigation is by full blood picture (infections/leukaemias), serology (infections/autoimmune diseases), FNA (to exclude metastatic cancer) and biopsy.

The preferred specimen for diagnosis, subtyping and grading of nodal malignant lymphoma is an excisional lymph node biopsy carefully taken by an experienced surgeon to ensure representation of disease and avoidance of traumatic artefact. Submission of the specimen fresh to the laboratory allows imprints to be made to which a wide panel of immunohistochemical antibodies can be applied, some of which are more effective than on tissue sections, e.g. demonstration of light chain restriction. Tissue can also be harvested for molecular and genetic techniques. Morphological classification is generally based on well-fixed, thin slices, processed through to paraffin with high quality 4-μm H&E sections. Core biopsy may be the only option if the patient is unwell or the lesion relatively inaccessible, e.g. mediastinal or para-aortic. Allowances must be made in interpretation for undergrading of nuclear size, sampling error and artefact. Confirmation of lymphomatous (or other) malignancy is the prime objective and further comments on subtyping and grading given with care and only if definitely demonstrable. A positive diagnosis can be given in a significant percentage of cases. Importantly, interpretation should be in light of the clinical context, i.e. the presence of palpable or radiologically proven significant regional or systemic lymphadenopathy and the absence of any obvious carcinoma primary site. Tumour heterogeneity must also be borne in mind. The same principles apply to FNAC, which is excellent at excluding inflammatory lymphadenopathy, e.g. abscess or sarcoidosis and non-lymphomatous cancer (e.g. metastatic squamous cell carcinoma, breast carcinoma or malignant melanoma) and reasonably robust at designating Hodgkin's and high-

grade non-Hodgkin's lymphoma. Morphology is the principal diagnostic criterion when assessing excisional lymph node biopsies, core biopsies and FNAs but is supplemented by immunohistochemical antibody panels targeted at the various diagnostic options, e.g. a small lymphoid cell proliferation (lymphocytic lymphoma vs. mantle lymphoma, etc). In addition, flow cytometry and molecular gene rearrangements are helpful in determining a diagnosis. Limited needle sampling techniques can also be used in patients with a previous tissue biopsy-proven diagnosis of lymphoma and in whom recurrence is suspected. However, possible transformation of grade must be considered and even change of lymphoma type, e.g. small lymphocytic lymphoma to Hodgkin's lymphoma or Richter's transformation to diffuse large B-cell lymphoma. A range of inflammatory nodal disease may also be encountered secondary to chemotherapy and immunosuppression, e.g. tuberculosis.

A systematic approach to excisional lymph node biopsies will allow the majority to be categorized as specific inflammatory pathology, benign or malignant and the latter as haematopoietic or non-haematopoietic. Diagnostic morphological clues to malignant lymphoma are:
Low-power magnification:

— capsular/extracapsular spillage of lymphoid tissue.
— capsular thickening and banded septal fibrosis or hyaline sclerosis.
— loss of sinusoids either with compression or due to a cellular infiltrate
— alteration in follicular architecture with changes in
  a. distribution: proliferation in the medulla
  b. size and shape: relative uniformity of appearance, and
  c. definition: loss of the mantle zone–germinal centre interface/"filling up" of the germinal centre/loss of tingible body macrophages.
— prominent post capillary venules

High-power magnification:

— presence of a background polymorphous inflammatory cellular infiltrate, e.g. eosinophils, plasma cells and histiocytes (epithelioid in character ± granulomas).
— alterations in the proportions of the normal cellular constituents.
— dominance of any mono- or dual cell populations.
— presence of atypical lymphoid cells
  a. nuclei: enlargement/irregularity/hyperchromasia/bi- or polylobation/mummification/apoptosis
  b. nucleoli: single/multiple/central/peripheral/eosinophilic/basophilic/Dutcher inclusions
  c. cytoplasm: clear/vacuolar/eosinophilic/scant/plentiful/paranuclear hof.

A morphological diagnostic short list should be created, e.g. mixed cellularity Hodgkin's disease vs. T-cell lymphoma vs. T-cell-rich B-cell lymphoma and a targeted immunohistochemical antibody panel used. In the majority of cases it will confirm the preliminary diagnosis but will in a minority lead to its modification and either a refinement within or revision of diagnostic category.

Regional lymphadenectomy comprises part of a formal cancer resection operation.

— size (cm) and weight (g)
— colour, consistency, necrosis.

2. HISTOLOGICAL TYPE AND DIFFERENTIATION/GRADE

Therapeutic and prognostic distinction is made between Hodgkin's and non-Hodgkin's malignant lymphoma, with a significant proportion of the former being reclassified as variants of the latter on the basis of improved immunophenotyping. Within classical Hodgkin's lymphoma there is a differentiation spectrum from nodular sclerosis through mixed cellularity to lymphocyte depleted, with the former divided into two subtypes that are of prognostic significance in limited stage disease. In non-Hodgkin's lymphoma better differentiated tumours are of a follicular pattern and small cell type and less differentiated lesions diffuse and large cell in character. This differentiation spectrum can predict the likelihood of untreated disease progression from indolence to aggressive behaviour but paradoxically often does not correlate with extent of disease stage, chemoresponsiveness, long-term disease-free survival and potential for cure. Thus, morphology with corroborative immunophenotyping (e.g. a Ki-67 proliferation index >90%) can identify those high-grade diagnoses requiring curative-intent high-dose multiagent chemotherapy, e.g. Burkitt's lymphoma, mediastinal large B-cell lymphoma, lymphoblastic lymphoma. As can be seen, size matters in grading, but not always as cell maturation (Burkitt's, lymphoblastic lymphoma) and aggressive behaviour linked to specific underlying chromosomal alterations (e.g. mantle cell lymphoma) must be taken into account. Thus the prognostic information used to determine treatment of lymphoma is provided by the histological subtyping and grading, supported by immunohistochemistry, the diagnostic importance of which varies with the lymphoma subtype, e.g. a significant contributor to diagnoses such as T-cell lymphoma and anaplastic large cell lymphoma. Molecular analysis is also of increasing importance in defining characteristic lymphoma types, treatment response and behaviour.

Non-Hodgkin's lymphoma

Non-Hodgkin's lymphoma (NHL) is classified according to the WHO/REAL (Revised European American Lymphoma Classification) system (Table 35.1), which defines each disease by its morphology, immunophenotype, genetic characteristics, proposed normal counterpart and clinical features, and is reproducible, with prognostic and therapeutic implications.

Hodgkin's lymphoma

WHO/REAL/RYE classification

Comprising nodular lymphocyte predominant Hodgkin's lymphoma (NLPHL—a B-cell lymphoma) and classic Hodgkin's lymphoma encom-

Table 35.1 WHO/REAL Classification of lymphoid neoplasms

B-cell neoplasms
Precursor B-cell neoplasms
  Precursor B-lymphoblastic lymphoma/leukaemia
Mature B-cell neoplasms
  Chronic lymphocytic leukaemia/small lymphocytic lymphoma
  B-cell prolymphocytic leukaemia
  Lymphoplasmacytic lymphoma/Waldenström's macroglobulinaemia
  Splenic marginal zone lymphoma
  Hairy cell leukaemia
  Plasma cell myeloma
  Solitary plasmacytoma of bone
  Extra-osseous plasmacytoma
  Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
  Nodal marginal zone B-cell lymphoma
  Follicular lymphoma
    Grading:
      Grade 1: 0 to 5 centroblasts per high power field*
      Grade 2: 6 to 15 centroblasts per high power field*
      Grade 3: greater than 15 centroblasts per high power field*
      Grade 3a: centrocytes are still present
      Grade 3b: centroblasts form solid sheets with no residual centrocytes
    Reporting of pattern:
      Follicular: greater than 75% follicular
      Follicular and diffuse: 25–75% follicular
      Focally follicular: less than 25% follicular
    Variants:
    Cutaneous follicle centre lymphoma
    Diffuse follicle centre lymphoma
      Grade 1: 0 to 5 centroblasts per high power field*
      Grade 2: 6 to 15 centroblasts per high power field*
  Mantle cell lymphoma
    Variants: Blastoid (classic or pleomorphic), others
  Diffuse large B-cell lymphoma
  Mediastinal (thymic) B-cell lymphoma
  Intravascular large B-cell lymphoma
  Primary effusion lymphoma
    Morphological variants:
      Centroblastic
      Immunoblastic
      T-cell/histiocyte-rich
      Anaplastic
  Burkitt's lymphoma
    Variants:
      Burkitt's lymphoma with plasmacytoid differentiation
      Atypical Burkitt/Burkitt-like
B-cell proliferations of uncertain malignant potential
  Lymphomatoid granulomatosis
  Post-transplant lymphoproliferative disorder, polymorphic

T-cell neoplasms
Precursor T-cell lymphomas
  Precursor T-lymphoblastic lymphoma/leukaemia
  Blastic NK-cell lymphoma

Table 35.1 *Continued*

T-cell neoplasms
Mature T-cell and NK-cell neoplasms
T-cell prolymphocytic leukaemia
Variants: small cell, cerebriform cell (Sézary cell-like)
T-cell granular lymphocyte leukaemia
Aggressive NK-cell leukaemia
Adult T-cell lymphoma/leukaemia (HTLV1+)
Clinical variants:
Acute
Lymphomatous
Chronic
Smoldering
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-type T-cell lymphoma
Variants: gamma-delta T-cell lymphoma in other anatomic sites (e.g. skin, intestine)
Subcutaneous panniculitic-like T-cell lymphoma
Blastic NK-cell lymphoma
Mycosis fungoides (MF) and Sézary syndrome
Variants:
Pagetoid reticulosis
MF-associated follicular mucinous
Granulomatous slack skin disease
Primary cutaneous anaplastic large cell lymphoma (C-ALCL)
Peripheral T-cell lymphoma, unspecified
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma
T-cell proliferation of uncertain malignant potential
Lymphomatoid papulosis

*Average over 10 hpfs.

passing nodular sclerosis, lymphocytic rich, mixed cellularity and lymphocyte depleted variants.

Lymphocyte and histiocyte (L and H) predominant—multilobated "popcorn" cell

— nodular: a B-cell lymphoma of early stage (cervical, axilla, groin) in young men and low-grade indolent behaviour with a 4% risk of diffuse large B-cell change.
— diffuse: a controversial category with overlap between lymphocyte-rich classic Hodgkin's lymphoma, vaguely nodular lymphocyte predominant Hodgkin's and other entities such as T cell/histiocyte-rich large B-cell NHL.

Classic Hodgkin's disease includes nodular sclerosis, lymphocyte-rich classical, mixed cellularity and lymphocyte depleted categories that vary in their clinical features, growth pattern, degree of fibrosis, background

cells, tumour cell numbers and atypia, and frequency of EBV infection, but not tumour cell immunophenotype.

Nodular sclerosis—lacunar cell
— birefringent fibrous bands (capsule and intranodal septa) with mixed inflammatory cell nodules containing lacunar cells, or cellular phase (rich in lacunar cells, scant fibrosis).
— *type 1.
— *type 2: lymphocyte depletion or pleomorphism of R–S (Reed–Sternberg) cells in more than 25% of nodules. An alternative descriptor is syncytial variant (sheets/clusters of R–S cells with central necrosis and a polymorph infiltrate).

Mixed cellularity
— R–S cells of classic type in a mixed inflammatory background. A category of exclusion in that no specific features of other subtypes are present.

Lymphocyte-rich classic
— scattered R–S cells against a nodular or diffuse background of small lymphocytes but no polymorphs.

Lymphocyte depleted
— R–S cells ± pleomorphism; diffuse fibrosis (fibroblasts obscure scattered R–S cells) and reticular variants (cellular, pleomorphic R–S cells).

Other features
— follicular and interfollicular Hodgkin's, Hodgkin's with a high epithelioid cell content.
— R–S cells: classic mirror image, binucleated cell with prominent eosinophilic nucleolus characteristic of mixed cellularity and lymphocyte depleted. Mononuclear, polylobated and necrobiotic (mummified) forms are also common. Lacunar cells (nodular sclerosis) can be mono-, bi- or polylobated (±necrobiotic), with characteristic perinuclear artefactual cytoplasmic retraction and clarity.

Immunophenotype
Lymphocyte predominant Hodgkin's

— popcorn cells: CD45/CD20/CD79a/EMA/J chain/bcl-6 positive, CD30 weak or negative, CD15 negative, EBV negative. Nuclear transcription factors Oct2/BoB1 positive.
— small lymphocytes: nodules of B cells (CD20) and intervening T cells (CD3).
— rosettes: CD57/CD4 positive T-cell rosettes around the popcorn cells.

Classic Hodgkin's disease

*Grade 1/grade 2 British National Lymphoma Investigation (BNLI).

— R–S cells: CD15/CD30 in 75%/90% of cases respectively, EBV (60–70% of cases), CD20/79a ±, CD45 negative.
— small lymphocytes: T cells (CD3/CD4).

In Hodgkin's lymphoma the heterogeneous cellular background (comprising 90% of the tissue) is an important part of the diagnosis: small lymphocytes, eosinophils, neutrophils, fibroblasts, histiocytes and follicular dendritic cells. Note that this is also seen in T-cell NHLs and T-cell-rich B-cell NHLs. Another differential diagnosis with which there can be overlap is anaplastic large cell lymphoma. Other features are progressive transformation of germinal centres (particularly associated with NLPHL), granulomas, necrosis, interfollicular plasma cells and reactive follicular hyperplasia, all of which should prompt a careful search for R–S cells.

Relatively common diagnostic difficulties in lymph node assessment are:

— follicular hyperplasia vs. follicular lymphoma.
— progressive transformation of germinal centres vs. NLPHL.
— T-cell hyperplasia vs. dermatopathic lymphadenopathy vs. T-cell lymphoma.
— Burkitt's lymphoma vs. Burkitt's-like diffuse large B-cell lymphoma.
— Hodgkin's lymphoma vs. anaplastic large cell lymphoma.
— post immunosuppression lymphoproliferative disorders.

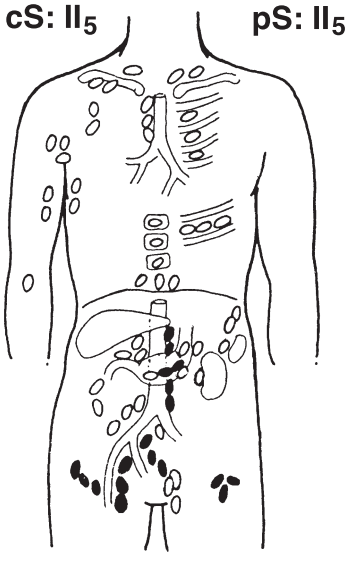
Important non-malignant differential diagnoses for malignant lymphoma are drug-induced (e.g. phenytoin) and viral reactive hyperplasia with paracortical transformation (e.g. infectious mononucleosis), and necrotizing and granulomatous lymphadenitis (Kikuchi's, toxoplasmosis).

3. EXTENT OF LOCAL TUMOUR SPREAD

Part of node or whole node.
Extracapsular into adjacent soft tissues or organ parenchyma.
A TNM classification is not used as the primary site of origin is often uncertain and attribution of N and M stages would therefore be arbitrary.

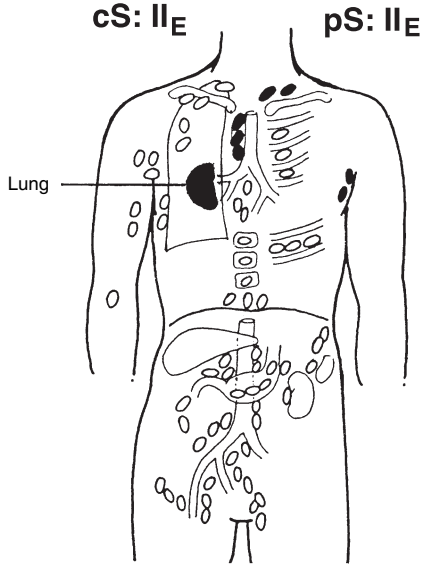
Stage: Ann Arbor classification

I Single lymph node region or localized extralymphatic site/organ
II Two or more lymph node regions on same side of the diaphragm or single localized extralymphatic site/organ and its regional lymph nodes ± other lymph node regions on the same side of the diaphragm
III Lymph node regions on both sides of the diaphragm ± a localized extralymphatic site/organ or spleen
IV Disseminated (multifocal) involvement of one or more extralymphatic organs ± regional lymph node involvement, or single extralymphatic organ and non-regional nodes.
  A Without weight loss/fever/sweats
  B With weight loss/fever/sweats:



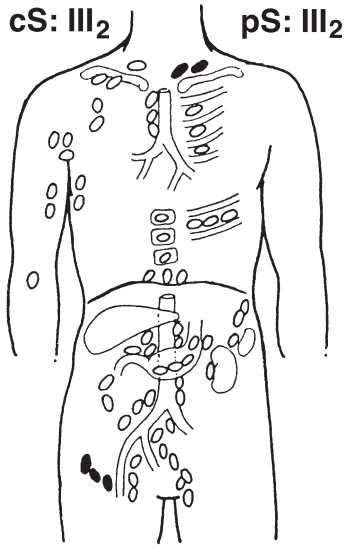
Two or more lymph node regions on the same side of the diaphragm

FIGURE 35.1. Malignant lymphoma.



A single extralymphatic organ or site and its regional node(s) ± other lymph node regions on the same side of the diaphragm

FIGURE 35.2. Malignant lymphoma.



Involvement of lymph node regions on both sides of the diaphragm (III) (Fig. 35.3), which may also be accompanied by localized involvement of an associated extralymphatic organ or site (III_E) (Fig. 35.4), or by involvement of the spleen (III_S), or both (III_{E+S}) (Fig. 35.5)

FIGURE 35.3. Malignant lymphoma.

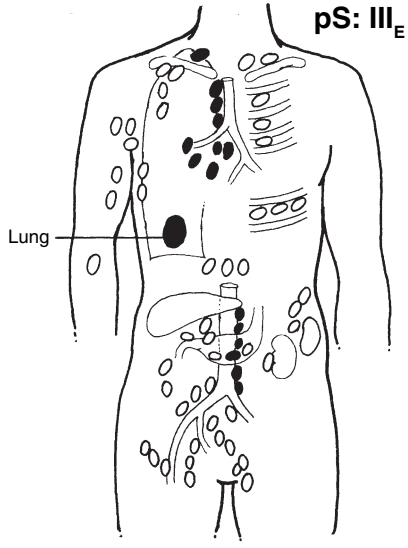


FIGURE 35.4. Malignant lymphoma.

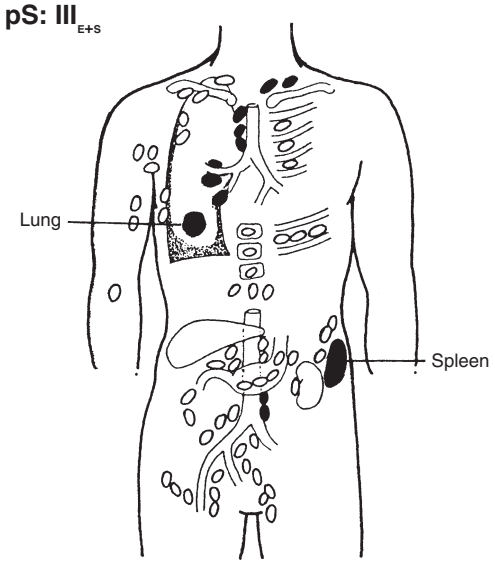


FIGURE 35.5. Malignant lymphoma.

fever >38°C
night sweats
weight loss >10% of body weight within the previous 6 months.

Subscripts, e.g.
- III_E denotes stage III with extranodal disease
- III_S denotes stage III with splenic involvement
- III_3 denotes stage III with involvement of 3 lymph node regions: >2 is prognostically adverse.

Lymph node regions:
- head, neck, face
- intrathoracic
- intra-abdominal
- axilla/arm
- groin/leg
- pelvis.

Other major structures of the lymphatic system are the spleen, thymus, Waldeyer's ring (palatine, lingual and pharyngeal tonsils), vermiform appendix and ileal Peyer's patches. Minor sites include bone marrow, liver, skin, lung, pleura and gonads.

Bilateral involvement of axilla/arm or inguinal/leg regions is considered as involvement of two separate regions.

Direct spread of lymphoma into adjacent tissues or organs does not alter the classification, e.g. gastric lymphoma into pancreas and with involved perigastric lymph nodes is stage II_E.

Involvement of two or more discontinuous segments of gastrointestinal tract is multifocal and classified as stage IV, e.g. stomach and ileum. However, multifocal involvement of a single extralymphatic organ is I_E.

Involvement of both organs of a paired site, e.g. lungs, is also I_E. Regional nodes for an extranodal lymphoma are those relevant to that particular side, e.g. gastric lymphoma—perigastric, left gastric, common hepatic, splenic and coeliac nodes.

Once the primary tissue diagnosis has been made staging laparotomy has been largely replaced by assessment of clinical and radiological parameters, e.g. abnormal liver function tests and imaging for hepato-/splenomegaly and lymphadenopathy. Bone marrow biopsy remains part of normal staging which is otherwise mostly clinical. Bone marrow or nodal granulomas per se are not sufficient for a positive diagnosis of involvement and diagnostic Hodgkin's cells are needed. Bone marrow involvement by NHL can be diffuse, nodular or focal and paratrabecular infiltration is a characteristic site.

4. LYMPHOVASCULAR INVASION

Present/absent.

Intra-/extratumoral.

Vessel wall invasion and destructive angiocentricity can be a useful indicator of malignancy in NHL and in specific subtypes, e.g. nasal angiocentric T/NK-cell lymphoma.

5. IMMUNOPHENOTYPE

In general an antibody panel is used with both expected positive and negative antibodies, and two antibodies per lineage. Commonly used antibodies available for formalin-fixed, paraffin-embedded sections are:

CD45:	pan-lymphoid and excellent in the characterization of a poorly differentiated malignant tumour, e.g. lymphoma vs. carcinoma vs. melanoma.
CD20:	routine B-cell marker. lymphoma cell positivity is a marker for specific rituximab monoclonal antibody therapy.
CD79a:	as for CD20 but also less mature (pre-B) cells.
CD3:	routine T-cell marker.
CD5:	T-cell marker and also some variants of B-cell lymphoma (lymphocytic and mantle cell lymphoma).
CD4, CD8:	T-cell subsets of use in some T-cell proliferations, e.g. mycosis fungoides. CD7 and granzyme C may also be of use in extranodal cases. Other T-cell markers include CD45R0 (UCHL1) and CD43 (MT1).
CD10:	lymphoblastic lymphoma (CALLA), Burkitt's lymphoma and follicle centre lymphoma. Also with CD5 and CD23 in the differential diagnosis of small B-cell lymphomas (lymphocytic CD5/CD23+: mantle cell CD5+: follicle centre cell CD10 +).

CD15, CD30:	classic Hodgkin's lymphoma R–S cells. CD30 is also positive in anaplastic large cell lymphoma and a proportion of diffuse large B-cell lymphomas.
CD56, CD57:	natural killer (NK) cells, e.g. angiocentric sinonasal lymphoma.
CD 38/138:	plasma cells and multiple myeloma (CD45/20 negative; CD79a±).
κ, λ light chains:	immunoglobulin light chain restriction is difficult to demonstrate satisfactorily in paraffin sections but more easily shown on fresh imprint preparations or by in-situ hybridization.
CD21, CD23:	follicular dendritic cells. CD23 also stains most B-cell lymphocytic lymphomas.
bcl-1/cyclin D1:	mantle cell lymphoma with the t (11:14) translocation. A nuclear epitope.
bcl-2:	many B-cell lymphomas including follicular (t(14:18) and others. Also normal B, T cells and negative in reactive germinal centres. Strong expression is adverse in diffuse large B-cell lymphomas.
bcl-6:	follicle centre lymphoma and a large proportion of diffuse large B-cell lymphomas.
Ki-67/MIB-1:	nuclear proliferation marker useful for identifying high-grade lymphomas, e.g. Burkitt's (98–100%), lymphoblastic lymphoma (also tdt positive) and diffuse large B-cell lymphoma with a high proliferation fraction.
EBV:	LMP-1 antibody is positive in a proportion of R–S cells in Hodgkin's lymphoma. In-situ hybridization for EBERs is more sensitive with a higher rate (60–70%) of positivity.
Tdt:	terminal deoxynucleotidyltransferase is positive in precursor B- and T-cell lymphoblastic lymphomas. A nuclear epitope.
CD1a:	Langerhans' cell histiocytosis.
ALK-1:	nucleophosmin-anaplastic lymphoma kinase fusion protein associated with the ALK-1 gene t(2:5) translocation and good prognosis anaplastic large cell lymphomas.

Molecular techniques

Immunoglobulin clonal heavy chain and T-cell receptor (TCR) gene rearrangements using polymerase chain reaction can be of use in difficult diagnostic cases, e.g. follicular hyperplasia vs. follicular lymphoma or T zone reactive hyperplasia vs. lymphoma. Also, where immunohistochemistry has been equivocal (e.g. dubious cyclin D1 staining in mantle cell lymphoma) chromosomal studies for specific translocations have a role to play. These techniques vary in their applicability to fresh tissue and routine paraffin sections and suitable arrangements for prompt

tissue transportation and referral on a regional network basis should be put in place. A majority of malignant lymphomas can be diagnosed without these techniques but their role is gradually evolving with respect to prognostication and therapy.

The evolution of new generation robust antibodies applicable to paraffin sections with unmasking of antigenic sites by antigen retrieval methods (microwave and pressure cooker techniques) has led to considerable reclassification of lymphomas with emergence of new entities. For example, lymphocyte depleted and mixed cellularity Hodgkin's lymphoma are diminishing as the full spectrum of NHL widens, viz. T-cell NHL, anaplastic large cell Ki 1 NHL, T-cell-rich B-cell lymphoma (<10% CD20 positive large cells on a background of CD3 small lymphocytes) . Unusually composite (HD/NHL) and borderline (HD/ALCL) cases also occur. It is important that a panel of antibodies is used and markers assessed in combination, e.g. in the sometimes difficult differential diagnosis of florid reactive hyperplasia vs. follicular lymphoma. Benign follicle centres are bcl-2 negative, contain CD68 positive macrophages, and show strong polar Ki-67 positivity whereas malignant follicles are diffusely bcl-2 positive with a low Ki-67 proliferation index (unless predominantly centroblastic) and absence of CD68 positive macrophages. Thus morphology and immunohistochemistry are used in tandem supplemented by molecular immunoglobulin and gene rearrangement studies. It should also be noted that clonality does not always correlate with progression to lymphoma, as has been demonstrated in some inflammatory skin, salivary and gastric biopsies.

Formalin fixation and high-quality, thin (4μm) paraffin sections are adequate for morphological characterization in most cases. Fixation should be sufficient (24–36h) but not excessive as this may mask antigenic sites.

Progressive transformation of germinal centres will sometimes subsequently develop nodular lymphocyte predominant Hodgkin's disease characterized by the emergence of popcorn or diagnostic R–S cells.

The majority (60–70%) of NHLs are large B-cell lymphomas and follicular lymphoma.

6. CHARACTERISTIC LYMPHOMAS

Precursor B cell lymphoblastic lymphoma/leukaemia.

— presents as childhood leukaemia or occasionally solid tumour (skin, bone, lymph node) and relapses in CNS/testis.
— 75% survival in childhood but only 20% in adults.
— medium sized round lymphoid cells with small nucleolus, mitoses.
— CD79a, CD10, tdt, CD99±, Ki-67 >95%, CD20±.

B-cell lymphocytic lymphoma/chronic lymphocytic leukaemia (CLL)

— adults with diffuse lymph node, bone marrow and blood involvement.
— small lymphocytes with pale proliferation centres (immunoblasts/prolymphocytes).

— CD45, CD20, CD5, CD23, bcl-2, Ki-67 <20%.
— Richter's transformation to large cell lymphoma in 3–5% of cases.
— occasional cases have Hodgkin's-like cells (CD30/15).

Lymphoplasmacytic lymphoma
— elderly involving marrow, nodes and spleen: indolent course.
— monoclonal IgM serum paraprotein with hyperviscosity symptoms and autoimmune/cryoglobulin phenomena.
— small lymphocytes, plasmacytoid and plasma cells.
— intranuclear Dutcher bodies.
— CD45 (CD5 and 10 negative).

Marginal zone lymphoma of MALT
— 8% of NHL, stomach 50% of cases, 80% stage I or II disease and indolent.
— usually extranodal associated with chronic autoimmune or antigenic stimulation.
— centrocyte-like cells, lymphocytes, plasma cells (scattered immunoblast/centroblast-like cells).
— destructive lymphoepithelial lesions, reactive germinal centres and follicular colonization.
— CD45, CD20 but CD5/10/23 negative.
— nodal variant is monocytoid B-cell lymphoma.
— gastric MALT with t(11:18) confers resistance to anti-Helicobacter treatment.

Hairy cell leukaemia
— elderly in bone marrow, spleen and lymph node.
— "fried egg" perinuclear cytoplasmic clarity with prominent cell boundaries.
— CD45, CD20, DBA44, tartrate resistant acid phosphatase (TRAP) positive.

Mantle cell lymphoma
— 6% of NHL.
— extensive disease including spleen, bone marrow, Waldeyer's ring ± bowel involvement (multiple lymphomatous polyposis).
— monomorphic small to medium sized irregular nuclei (centrocytic). Rare immunoblastic variant.
— diffuse with vague architectural nodularity.
— CD45, CD20, and typically CD5/cyclin D1 (t11:14) /CD43 positive.
— CD10, CD23 negative.
— aggressive with mean survival of 3–5 years.

Follicular (follicle centre) lymphoma
— 40% adult NHL and transformation to diffuse large B-cell lymphoma is relatively common.
— patterns: follicular, follicular and diffuse, diffuse (see Table 35.1).

— cell types: centroblasts with large open nuclei, multiple small peripheral basophilic nucleoli, variable cytoplasm.
centrocytes with medium sized irregular nuclei.
— grade: 1/2/3 according to the number of centroblasts per hpf (see Table 35.1). Grade 3 has high Ki-67 and bcl-2 may be negative.
— CD45, CD20, CD10 (60%), bcl-2 (t14:18; 70–95%), bcl-6.
— usually CD21/23 positive and CD5 negative.
— high-stage disease (bone marrow 40% of cases) and indolent time course but late relapse (5–10 years) with large cell transformation.
— pattern and grade can vary within a node necessitating adequate sampling.

Diffuse large B-cell lymphoma
— 30–40% adult NHL, 40% extranodal (especially stomach, skin, CNS, bone, testis etc).
— centroblasts, immunoblasts (prominent central nucleolus), bi-/polylobated, cleaved, anaplastic large cell, plasmablastic forms, basophilic cytoplasm.
— variants: T cell/histiocyte rich, mediastinal/thymic, intravascular, primary effusion, primary CNS.
— CD45, CD20, CD79a, Ki-67 40–90%, CD10 (40%), bcl-2 (30%), bcl-6, CD5/23/CD30±.
— strong bcl-2 expression is adverse.
— diffuse large B-cell lymphomas of germinal centre origin (CD10+, or CD10–/bcl-6+/MUM1–) are of better prognosis (76% 5-year survival) than those of non-germinal centre origin (CD10–/bcl-6– or CD10–/bcl-6+/MUM1+: 34% 5-year survival). "Germinal centre markers" include CD10, bcl-6, CD21 and CD23, while MUM-1 (Interferon Regulating Factor 4: IRF4) is expressed by post germinal centre destined B cells.

Burkitt's lymphoma
— 2.5% NHL.
— childhood or young adult; endemic/sporadic/AIDs related (EBV: 95%/15–20%/30–40% of cases, respectively).
— jaw and orbit (early childhood/endemic), or abdomen (ileocaecal/ovaries/late childhood or young adult/sporadic) and breasts with risk of CNS involvement.
— monomorphic, medium-sized lymphoid cells, multiple small central nucleoli, basophilic cytoplasm.
— mitoses, apoptosis, "starry-sky" pattern.
— CD79a, CD20, CD10, bcl-6, Ki-67 98–100% and bcl-2/tdt/CD5/23 negative.
— t(8:14) and t(2:8)/t(8:22) variants. Demonstration of t(8:14) requires fresh tissue.
— requires aggressive polychemotherapy and potentially curable.

Peripheral T-cell lymphoma, unspecified
— 10% NHL.
— interfollicular/paracortical or diffuse infiltrate.

— variable nuclear morphology from medium-sized centrocyte-like to blast cells, "crows-feet" appearance.
— cytoplasmic clearing.
— accompanying eosinophils, histiocytes and vascularity with prominent post capillary venules.
— lymphoepithelioid variant (Lennert lymphoma).
— usually CD3, CD4, CD5 and TCR gene rearrangements, sometimes CD8/CD30/CD56.
— worse prognosis than B-cell lymphomas.
— variants: angioimmunoblastic T-cell lymphoma (CD3, CD4, CD8,TCR (75%), high endothelial venules, prominent dendritic cells).
mycosis fungoides/Sézary syndrome (usually CD3, CD5, TCR and CD4+/CD8–).
enteropathy-type T-cell lymphoma (pleomorphic, CD3, associated gluten enteropathy or ulcerative jejunitis).
subcutaneous panniculitis-like T-cell lymphoma (nodules trunk/extremities, CD3, CD8, TCR).

Extranodal NK/T-cell lymphoma, nasal type
— necrotizing lethal midline granuloma.
— polymorphic inflammatory infiltrate of eosinophils and histiocytes which may obscure tumour cells.
— variably sized atypical lymphoid cells, EBV positive on in-situ hybridization.
— angiocentric and destructive.
— variably CD2, CD56, CD45R0, TCR–. Cytoplasmic but not surface CD3.

Anaplastic large cell lymphoma
— 2.5% NHL.
— elderly and young (25% < 20 years): ALK negative and ALK positive/males, respectively.
— may also follow mycosis fungoides, lymphomatous papulosis or Hodgkin's lymphoma.
— cohesive, sinusoidal growth pattern of "epithelioid" cells mimicking carcinoma, melanoma and germ cell tumour.
— large pleomorphic nuclei, multiple nucleoli, polylobated forms, "hallmark cells" with horseshoe or reniform nucleus; rarely small cell variant.
— CD30, and EMA/CD45/CD3±.
— mainly T (60–70% TCR), B (0–5%) and null (20–30%) cell types.
— 12–50% of adult cases are t(2:5) and ALK-1 positivity confers a good prognosis (80% 5-year survival) despite presentation with stage III/IV disease.

Precursor T-lymphoblastic lymphoma/leukaemia
— CD3, CD4, CD8, Ki-67 >95%, tdt; presents in childhood/adolescence as a mediastinal mass (also nodes, skin, liver, spleen, CNS, gonads).

Granulocytic sarcoma

— myelomonocytic markers are CD68, myeloperoxidase, chloroacetate esterase, neutrophil elastase, lysozmye, CD15, CD34, CD43.

7. EXTRANODAL LYMPHOMA

Of NHLs, 25–40% are extranodal, defined as when a NHL presents with the main bulk of disease at an extranodal site usually necessitating the direction of treatment primarily to that site. In order of decreasing frequency sites of occurrence are:

— gastrointestinal tract (especially stomach then small intestine)
— skin
— Waldeyer's ring
— salivary gland
— thymus
— orbit
— thyroid
— lung
— testis
— breast
— bone.

A majority are aggressive large B-cell lymphomas, although T-cell lesions also occur (cutaneous T-cell lymphoma, enteropathy-associated T-cell lymphoma, NK/T-cell sinonasal lymphoma). Their incidence is rising partly due to increased recognition and abandonment of terms such as pseudolymphoma, but also because of aetiological factors, e.g. AIDS, immunosuppression after transplantation or chemotherapy, autoimmune diseases and infections (H. pylori, EBV, hepatitis C virus).

Many are low-grade in character with indolent behaviour, remaining localized to the site of origin. However, a significant proportion present as or undergo high-grade transformation and when they metastasize typically do so to other extranodal sites. This site homing can be explained by the embryological development and circulation of mucosa-associated lymphoid tissue (MALT). The low-grade MALTomas often arise from a background of chronic antigenic stimulation:

gastric lymphoma	H. pylori gastritis
thyroid lymphoma	Hashimoto's thyroiditis
salivary gland lymphoma	lympho(myo-)epithelial sialadenitis/ Sjögren's syndrome.

Their classification does not strictly parallel that of nodal lymphoma but mirrors marginal zone or monocytoid B-cell lymphoma. They normally comprise a sheeted or nodular infiltrate of centrocyte-like cells, destructive lymphoepithelial lesions and monotypic plasma cell immunoglobulin expression with interfollicular infiltration or follicular colonization of reactive follicles by the neoplastic cells. There is often a component of blast cells and the immunophenotype is one of exclusion in that they are CD5 and cyclin-D1 negative, ruling out mantle cell lymphoma and other

small B-lymphocyte lymphoproliferative disorders. Other extranodal lymphomas have diverse morphology and immunophenotype correlating with the full spectrum of the WHO/REAL classifications, although the node-based categories are not consistently transferable to extranodal sites.

Immunosuppressed post-transplant (solid organs or bone marrow) patients are prone to a wide spectrum of nodal/extranodal EBV-associated polyclonal and monoclonal B-cell lymphoproliferative disorders (PTLD). Three main categories exist: plasmacytic hyperplasia/infectious mononucleosis-like (low-grade PTLD), polymorphic B-cell hyperplasia/polymorphic B-cell lymphoma (intermediate-grade PTLD) and monomorphic immunoblastic or centroblastic lymphoma/multiple myeloma (high-grade PTLD). There is considerable overlap between the categories but in general monomorphic/monoclonal lesions are worse than polymorphic/polyclonal lesions. However, even what appears to be high-grade lymphoma may potentially regress if immunosuppressant therapy is decreased. Serum titres and/or tissue expression of EBV are ascertained and clinical response to alteration of immunotherapy and anti-viral therapy assessed prior to use of chemotherapy. Similar findings can also be present in patients receiving chronic immunosuppression therapy for autoimmune and rheumatological disorders.

8. PROGNOSIS

Chemotherapy and radiotherapy are the two principal treatment modalities for malignant lymphoma but surgical excision is often involved for definitive subtyping in primary nodal disease or for removal of a bleeding or obstructing tumour mass and primary diagnosis of extranodal lymphoma, e.g. gastric lymphoma. Prognosis relates to lymphoma type (small cell and nodular are better than large cell and diffuse) and stage of disease. Low-grade or indolent nodal lymphomas have a high frequency (>80% at presentation) of bone marrow and peripheral blood involvement and are incurable, pursuing a protracted time course and relapse at a late date (5–10 years) with potentially blast transformation (e.g. CLL: 23% risk at 8 years). High-grade or aggressive lymphomas develop bone marrow or peripheral involvement as an indication of advanced disease and are fatal within 1–2 years if left untreated. Prior to this the majority show good chemoresponsiveness with complete remission in 80% and potential cure in 60%. Overall, four broad prognostic categories are identified in NHL, although outlook does vary within individual types, e.g. grades I/II or III follicle centre (follicular) lymphoma:

NHL type	5-year survival
1. Anaplastic large cell/MALT/follicular	>70%
2. Nodal marginal zone/small lymphocytic/lymphoplasmacytoid	50–70%
3. Mediastinal B cell/large B cell/Burkitt's	30–50%
4. T lymphoblastic/peripheral T cell/mantle cell	<30%

Hodgkin's lymphoma is relatively radiotherapy and chemotherapy responsive. Prognosis relates to histological category (e.g. type 2 nodular

sclerosis is worse than type 1) but, more importantly, stage of disease. Average 5-year survival rates for Hodgkin's lymphoma are 75% with worse outcome for older patients (>40–50 years), disease of advanced stage (i.e. more than one anatomical site), involvement of the mediastinum by a large mass (>1/3 of the widest thoracic diameter), spleen or extranodal sites. Lymphocyte-depleted Hodgkin's lymphoma is least favourable, with the mixed cellularity category being of intermediate outlook and both usually presenting with high-stage disease involving spleen, retroperitoneal nodes and abdominal organs. However, histological type is usually regarded as having prognostic value only in limited (stage I or II) disease. Hodgkin's disease has a bimodal age presentation (15–40 years, 60–70 years) with nodular sclerosis type in the head and neck of young people being the commonest (75% of cases). About 25% of patients have prognostically adverse B cell symptoms at presentation, but the commonest complaint is painless cervical lymphadenopathy ± mediastinal disease. Disease usually involves contiguous, axial lymph node groups (neck, axilla, mediastinum, retroperitoneum, groin) with occasional extranodal involvement.

There is evidence that early (confined to the mucosa), low-grade gastric MALToma is potentially reversible on removal of the ongoing antigenic stimulus, i.e. antibiotic treatment of H. pylori. However, high-grade disease or low-grade lesions with deep submucosal or muscle invasion require chemotherapy supplemented by surgery if there are local mass effects, e.g. bleeding or pyloric outlet stenosis. Prognosis of MALT-derived NHL relates to the histological grade and stage of disease.

T-cell lymphomas form a minority of NHL (10–15%) and tend to have a worse prognosis than B-cell lesions. Their cytological features are not particularly reliable at defining disease entities or clinical course, which is more dependent on tumour site and clinical setting. Involvement of extranodal sites and relapse is not infrequent with typically an aggressive disease course, e.g. enteropathy-type T-cell lymphoma and T/NK (angiocentric) sinonasal lymphoma. Cutaneous ALCL has a favourable prognosis while that of systemic ALCL with skin involvement is poor: 50% present with stage III/IV disease and there is a 65–85% 5-year survival rate, but relapse is high (30–60%).

Similarly some B-cell lymphomas have site-specific characteristics and clinical features, e.g. mantle cell lymphoma in the gut (lymphomatous polyposis) or diffuse mediastinal large B-cell lymphoma—young females with a rapidly enlarging mediastinal mass associated with superior vena cava syndrome. A large (>10 cm) mass and extramediastinal spread indicate poor prognosis. Generally adverse prognostic factors in NHL are:

— age > 60 years.
— male gender.
— systemic symptoms (fever >38°C, weight loss >10%, night sweats).
— poor performance status.
— elevated serum LDH.
— tumour bulk:
  5–10 cm (stage I/II); >10 cm (stage III/IV)

large mediastinal mass
palpable abdominal mass
combined para-aortic and pelvic nodal disease.

9. OTHER MALIGNANCY

Carcinoma, germ cell tumours and malignant melanoma frequently metastasize to lymph nodes and are seen either in diagnostic biopsies (or FNAC) in patients with lymphadenopathy or in regional lymph node resections in patients with known cancer. Spread of sarcoma to nodes is unusual, although it does occur, e.g. alveolar rhabdomyosarcoma, epithelioid sarcoma, synovial sarcoma. Assessment is by routine morphology supplemented by ancillary techniques, e.g. immunohistochemistry and polymerase chain reaction methods, although it should be noted that the significance of nodal micrometastases in a number of cancers is still not resolved. Metastases are initially in the subcapsular sinus network expanding to partial or complete nodal effacement with potential for extracapsular spread. Anatomical site of involvement can be a clue as to the origin of the cancer, e.g. neck (cancer of the upper aerodigestive tract, salivary glands or thyroid gland), supraclavicular fossa (lung, stomach, prostate or breast cancer), axilla (breast cancer or malignant melanoma), groin (cancer of the perineum or perianal area, cutaneous melanoma and rarely the pelvis) and retroperitoneum (germ cell tumour). The metastatic deposit may be necrotic or cystic (e.g. squamous cell carcinoma of the head and neck), resemble the primary lesion or be more or less well differentiated. Cell cohesion with nesting, necrosis, focal or sinusoidal distribution, solid lymphatic plugs of tumour and plentiful cytoplasm favour non-lymphomatous neoplasia, although this is not always the case, e.g. anaplastic large cell lymphoma or diffuse large B-cell lymphoma. In this respect, a broad but basic panel of antibodies is crucial for accurate designation (e.g. cytokeratins, CD45, CD30, S100, melan-A, chromogranin) supplemented by histochemistry (e.g. PAS diastase resistant mucin positivity, an organoid pattern of reticulin fibres). Some metastases also induce characteristic inflammatory responses, e.g. squamous cell carcinoma of head and neck, large cell lung cancer and nasopharyngeal carcinoma (lymphocytes, eosinophils, granulomas) even mimicking Hodgkin's disease. Some diagnostic clues are:

— malignant melanoma: cell nests, eosinophilic nucleolus, spindle/epithelioid cells, melanin pigment, S100, HMB-45, melan-A.
— germ cell tumour: midline (mediastinum or retroperitoneum), elevated serum βHCG or AFP (± tissue expression), PLAP/CD117 (seminoma), cytokeratins/CD30 (embryonal carcinoma).
— lobular breast cancer: sinusoidal infiltrate of sheeted, non-cohesive small cells, intracytoplasmic lumina, cytokeratins (CAM5.2, AE1/AE3, CK7),

	GCDFP-15 and ER positive. Metastatic ductal cancer often has a nested pattern of larger cells with variable ER/Her-2 positivity (Grade 1 or 2 tumours may have a tubular component).
— small cell carcinoma:	small (×2–3 the size of a lymphocyte), round to fusiform cells, granular chromatin, inconspicuous nucleolus, moulding, crush and DNA artefact, ± paranuclear dot CAM5.2, and chromogranin/synaptophysin/CD56/TTF-1/Ki67 (Merkel cell carcinoma is CK20 positive). In addition to positivity with the above markers, other metastatic neuroendocrine tumours (e.g. carcinoid, large cell neuroendocrine carcinoma) show stronger cytokeratin expression than small cell carcinoma.
— lung adenocarcinoma:	variably glandular or tubulopapillary, CK7/TTF-1/CEA/BerEP4/MOC31.
— thyroid carcinoma:	papillae, characteristic nuclei (optically clear, grooves), psammoma bodies, CK7/TTF-1/thyroglobulin.
— colorectal adenocarcinoma:	glandular with segmental and dirty necrosis, CK20/CEA/CDX-2.
— upper gastrointestinal and pancreaticobiliary adenocarcinoma:	tubuloacinar, tall columnar cells with clear cytoplasm, CK7/CEA/CA19-9/± CK20/CDX-2.
— ovarian carcinoma:	serous (tubulopapillary, psammoma bodies, CK7/CA125/WT-1) or mucinous (glandular, CK7, ± CK20/CA125).
— uterine adenocarcinoma:	endometrioid (CK7/vimentin/PTEN/ER) or serous (CK7/p53).
— prostate adenocarcinoma:	acinar or cribriform, PSA m/p, PSAP.
— bladder carcinoma:	nested (squamoid) or micropapillary, CK7/CK20/34βE12/uroplakin.

m, monoclonal; p, polyclonal.

The reader is referred to the Introduction for further discussion of the use of immunohistochemistry.

Bone and Soft Tissue Cancer

- Bone and Soft Tissue Sarcomas (with comments on retroperitoneum and adrenal gland)

36

Bone and Soft Tissue Sarcomas (with comments on retroperitoneum and adrenal gland)

1. GROSS DESCRIPTION

Specimen

— fine needle aspirate/needle core biopsy/open biopsy (incisional/curettings)/enucleation/wide local excision/compartmentectomy/segmental resection/en-bloc resection/amputation (limb (below/above knee, etc))/complex resection (forequarter/hindquarter/hemipelvectomy).
— right or left.
— size (cm) and weight (g).
— bone tumours often present as severe continuous pain unrelieved by anti-inflammatory agents, swelling or sometimes as a pathological fracture following low-impact trauma. Investigation is by plain X-ray and CT scan looking particularly for signs of periosteal reaction. A tissue diagnosis is obtained by needle core biopsy under radiological control. Osteosarcoma and Ewing's sarcoma are treated by a combination of chemotherapy and surgery, chondrosarcoma by surgery. Most primary bone tumours arise de novo but a minority occur in association with recognizable precursors, e.g. Paget's disease or a history of radiation. Metastatic bone disease can cause hypercalcaemia and is detected by isotope bone scan. Benign soft tissue tumours far outnumber malignant cases. Soft tissue sarcomas occur mainly in the extremities (often thigh) but also the retroperitoneum and trunk wall. They are usually deep seated and progressively increase in size, causing a lump or swelling and sometimes pain with a loss of function in the limb or adjacent organs. Plain X-ray may show focal calcification (e.g. synovial sarcoma) but MRI is the investigation of choice in defining the nature of the mass, its extent and involvement of adjacent structures. CT scan is used for lesions of the trunk. After full clinical and radiological assessment most centres use needle core biopsy to obtain a tissue diagnosis and open biopsy only when needle core biopsy or FNA have proven inconclusive. Surgery is the mainstay of treatment with mainly chemotherapy for Ewing's sarcoma and rhabdomyosarcoma.

Tumour

Site
— osseous: paracortical (paraosteal/periosteal); cortical; medullary (epiphysis/metaphysis/diaphysis); soft tissue extension.
— soft tissues: dermis/subcutaneous tissue/deep fascia/peripheral nerve/muscle/osseous extension/retroperitoneal.
— satellite nodules: size (cm) and distance (cm) from the main tumour.
— location: may be indicative, e.g. pelvis—Ewing's sarcoma or chondrosarcoma; chest wall—Askin (thoracopulmonary neuroectodermal) tumour, alveolar rhabdomyosarcoma.

Size
— length × width × depth (cm) or maximum dimension (cm).

Appearance
— solid/cystic/necrotic/lobulated/fatty/myxoid/cartilaginous/osseous.

Edge
— circumscribed/irregular.

Vessels
— relationship of tumour to vessels.

2. HISTOLOGICAL TYPE

Prior to histological evaluation of any bone or soft tissue sarcoma the pathologist must be aware of the patient's age, anatomical site of the lesion, subsite (e.g. epiphysis, metaphysis or diaphysis of bone) and, crucially, the radiological appearances. For example, a rapidly growing chest wall lesion in a young male may be nodular fasciitis rather than a sarcoma, peripheral chondroid lesions are benign whereas proximal are more likely to be malignant, and an epiphyseal lesion is likely to be a giant cell tumour (adult) or chondroblastoma (child) rather than an osteosarcoma (young/metaphysis). Age also closely correlates with type of soft tissue sarcoma: embryonal rhabdomyosarcoma (infants), synovial sarcoma (young adult), liposarcoma (middle age) and malignant fibrous histiocytoma (elderly). Close clinicopathological correlation is fundamental to the diagnosis.

Osteo-, chondro-, Ewing's/PNET, lipo-, synovial-, fibro-, rhabdo-, leiomyo-, angio-, malignant peripheral nerve sheath tumours, malignant fibrous histiocytoma and variants are amongst the main categories of sarcoma and each comprises variable numbers of subtypes (Tables 36.1 and 36.2).

Morphology is the mainstay of diagnosis but a panel of immunohistochemical antibodies to intermediate filaments and other markers (e.g. alkaline phosphatase on fresh tissue touch imprints for osteosarcoma), electron microscopy and cytogenetic analysis should be used as appropriate. This allows subclassification as to histogenetic type for a

Table 36.1 Bone neoplasms (ADASP Guidelines)

Adamantinoma
  Conventional
  Osteofibrous-dysplasia-like (well differentiated)
Angiosarcoma
Chondrosarcoma
  Conventional
  Clear cell
  Dedifferentiated
  Mesenchymal
  Peripheral juxtacortical (periosteal)
  Myxoid
  Arising in association with osteochondroma
  Other
Chordoma
  Conventional
  Chondroid
  Dedifferentiated
Ewing's sarcoma/peripheral neuroectodermal tumour (PNET)
Fibrosarcoma
  Conventional
  Periosteal
Giant cell tumour of bone (specify: conventional, malignant)
Haemangioendothelioma
  Epithelioid
Haemangiopericytoma/solitary fibrous tumour
Leiomyosarcoma
Liposarcoma
Malignant fibrous histiocytoma
Malignant mesenchymoma
Malignant peripheral nerve sheath tumour
Osteosarcoma
  Conventional
  Chondroblastic
  Fibroblastic
  Osteoblastic
  Mixed (specify cell types)
  Low grade central
  Intraosseous, well differentiated
  Giant cell rich
  Small cell
  Telangiectatic
  Epithelioid
  Osteoblastoma-like
  Chondroblastoma-like
  Associated with (specify: fibrous dysplasia, Paget's disease of bone)
  Post-radiation
Surface
  Parosteal
  Dedifferentiated parosteal
  Periosteal
  High grade surface
Rhabdomyosarcoma

Table 36.2 Soft Tissue Sarcomas (ADASP Guidelines)

Adipocytic tumours
- Atypical lipomatous tumour/well-differentiated liposarcoma
  - (a) lipoma-like
  - (b) sclerosing
  - (c) inflammatory
  - (d) spindle cell
- Dedifferentiated liposarcoma
- Myxoid/round cell liposarcoma
- Pleomorphic liposarcoma

Fibrous/myofibroblastic tumours
- Solitary fibrous tumour (includes haemangiopericytoma)
- Inflammatory myofibroblastic tumour
- Dermatofibrosarcoma protuberans
- Low-grade myofibroblastic sarcoma
- Myxoinflammatory fibroblastic sarcoma
- Infantile fibrosarcoma
- Adult fibrosarcoma
- Myxofibrosarcoma
- Low-grade fibromyxoid sarcoma
- Sclerosing epithelioid fibrosarcoma

Fibrohistiocytic tumours
- Plexiform fibrohistiocytic tumour
- Giant cell tumour of soft tissue
- Undifferentiated pleomorphic sarcoma/pleomorphic "MFH"
- Undifferentiated pleomorphic sarcoma with giant cells/giant cell "MFH"
- Undifferentiated pleomorphic sarcoma with prominent inflammation/ inflammatory "MFH"
- Malignant tenosynovial giant cell tumour

Smooth muscle tumours
- Leiomyosarcoma

Perivascular tumours
- Malignant glomus tumour

Skeletal muscle tumours
- Rhabdomyosarcoma
  - (a) embryonal
  - (b) botryoid
  - (c) spindle cell
  - (d) alveolar
  - (e) pleomorphic

Vascular tumours
- Kaposi sarcoma
- Epithelioid haemangioendothelioma
- Angiosarcoma (includes lymphangiosarcoma)

Neuroectodermal tumours
- Malignant peripheral nerve sheath tumour
  - with heterologous rhabdomyosarcoma (Triton tumour)
  - with (specify other mesenchymal heterology)
  - epithelioid variant
- Malignant granular cell tumour
- Malignant melanotic schwannoma
- Malignant peripheral primitive neuroectodermal tumour (PNET, extraskeletal Ewing's sarcoma)

Table 36.2 *Continued*

Extraskeletal chondro-osseous tumours
Extraskeletal mesenchymal chondrosarcoma
Extraskeletal osteosarcoma
Tumours of uncertain differentiation
Angiomatoid "MFH"
Ossifying fibromyxoid tumour
Myoepithelioma/mixed tumour
Alveolar soft part sarcoma
Epithelioid sarcoma
Synovial sarcoma
Extraskeletal myxoid chondrosarcoma
Clear cell sarcoma (malignant melanoma of soft parts)
Desmoplastic small cell tumour
Extrarenal rhabdoid tumour
Intimal sarcoma
PEComa
Malignant mesenchymoma

majority of lesions with, by exclusion, a minority of pleomorphic sarcomas designated malignant fibrous histiocytoma. Most soft tissue sarcomas arise from primitive multipotential mesenchymal cells which can differentiate along one of several lines resulting in histological overlap. One morphological approach is to categorize lesions as

a. predominantly spindle cell with various patterns: e.g. monomorphic fibrosarcomatous (synovial sarcoma) or pleomorphic—MFH like (pleomorphic liposarcoma)
b. spindle cells mixed with other mesenchymal elements: e.g. liposarcoma (fat), synovial sarcoma (epithelial component) or myxoid liposarcoma (myxoid material).
c. round cell morphology: e.g. PNET and rhabdomyosarcoma (small cells), clear cell sarcoma (large cells) or desmoplastic small round cell tumour (rhabdoid cells).

Diagnostic pointers to sarcoma can be general or distinctive. The former include deep-seated anatomical location, progressive increase in size, irregularity of margins, cellularity, atypia, necrosis, mitotic activity and vascular invasion. Some distinctive features are:

Liposarcoma

well differentiated:	variation in adipocyte size and shape multivacuolar lipoblasts atypical mesenchymal nuclei in broad connective tissue septa.
myxoid:	myxoid stroma with signet ring lipoblasts plexiform capillary network ± a high-grade round cell component (epithelioid cells/cords/trabeculae).

dedifferentiated: spindle cell or MFH patterns overlapping with pleomorphic liposarcoma.

Leiomyosarcoma
Usually a monomorphic spindle cell tumour and a fibrosarcomatous pattern of cells with tapering eosinophilic cytoplasm and blunt-ended nuclei. Mitoses, atypia and necrosis may not be prominent so anatomical location and radiological findings are important. Forms a significant proportion of retroperitoneal sarcomas and may also arise from large blood vessels, e.g. inferior vena cava. Epithelioid and myxoid variants occur.

Synovial sarcoma
Either classical biphasic with a glandular epithelial component and background spindle cells or monophasic with a fibrosarcomatous spindle cell pattern. Focal microcalcification.

Malignant fibrous histiocytoma (MFH)
Storiform (cartwheel/whorls) or fascicular spindle cell patterns. Mononuclear, osteoclast type and bizarre pleomorphic giant cells are not uncommon.

Dermatofibrosarcoma protuberans (DFSP)
Uniform, moderately cellular dermal plaque of spindle cells in a storiform pattern with lace-like infiltration of subcutaneous fat.

Malignant peripheral nerve sheath tumour (MPNST)
Monophasic fibrosarcomatous pattern with prominent nodularity and entrapped nerves at the tumour periphery. Can be epithelioid in character or include a biphasic glandular epithelial component. 50% arise in von Recklinghausen's disease.

Angiosarcoma
Branching vasoformative network dissecting collagen and lined by abnormal endothelial cells. Intracytoplasmic vacuoles containing red blood cells.

Kaposi's sarcoma
Cutaneous or visceral mucosal with patch, plaque and tumour stages. Nodules of spindle cells (± hyaline globules) and slit-like spaces containing red cells.

Epithelioid sarcoma
Nodular dermal/subcutaneous lesion in the hand/wrist of young adults with a "pseudonecrobiotic granulomatous" pattern of CAM5.2/EMA positive spindle/epithelioid cells.

Clear cell sarcoma of tendon sheath
Nests of S100 positive polygonal/fusiform cells in dense collagen septate stroma. Often in the foot or ankle of young adults.

Alveolar soft part sarcoma
Organoid nests of large eosinophilic cells with central dyscohesion giving an alveolar pattern. Cytoplasmic PAS-diastase positive rhomboidal crystals. Extremities in adults, head and neck in children.

Fibrosarcoma
Relatively unusual and only after excluding other sarcomas with a fibrosarcomatous pattern. Fibroblast bundles in a herring bone pattern with variable collagen content.

Small round cell tumours
More often in children and young adults including Ewing's sarcoma/PNET (pelvis, long bones, ribs), rhabdomyosarcoma (alveolar and embryonal subtypes) and desmoplastic small round cell tumour (abdominopelvic area/peritoneum with nests of cells in a prominent collagenous stroma). To be distinguished by characteristic anatomical locations and immunophenotype from other small cell malignancy, e.g. neuroblastoma, lymphoma/leukaemia, small cell malignant melanoma or osteosarcoma and small cell carcinoma. Pleomorphic rhabdomyosarcoma is a rare high-grade sarcoma in the deep soft tissues of the lower extremities of adults.

Chondrosarcoma
Axial location in older adults and hypercellular hyaline cartilage with atypical chondrocyte nests and nuclei. Infiltrative, lobulated and pushing margin into bone medulla, cortex or soft tissues. Grading is prognostically important. Also clear cell, myxoid, mesenchymal and dedifferentiated variants.

Osteosarcoma
Metaphysis/diaphysis in long bones of children or young adults and infiltrative and destructive with elevation of the periosteum. Variably pleomorphic spindle cells associated with formation of osteoid matrix. There are a number of variants including osteoblastic, chondroblastic, fibroblastic, giant cell, small cell and telangiectatic. Also low-grade central (medullary) and parosteal forms, and, intermediate periosteal and high-grade surface osteosarcomas.

A monomorphic or pleomorphic spindle cell tumour in breast, bowel or other viscera is usually a sarcomatoid carcinoma, and in skin or lymph node metastatic melanoma. A similar soft tissue lesion is usually a sarcoma, but metastatic melanoma, carcinoma and lymphoma must be considered and excluded.

Metastatic carcinoma is the commonest malignant tumour of bone, typical primary sites being lung, kidney, breast, prostate and thyroid. It can be single or multiple, 70% affect the axial skeleton, and metaphysis is the preferred site.

3. DIFFERENTIATION/GRADE
Well/moderate/poor, or Grade 1/2/3.

— based on the degree of resemblance to adult mesenchymal tissues, cytological atypia, necrosis and mitotic activity with grade 1/well differentiation equating to low-grade, and grade 2/moderate and grade 3/poor differentiation to high-grade.

Low-grade/high-grade. Some lesions define their own grade by way of their inherent clinical behaviour:

— high-grade: Ewing's sarcoma/peripheral neuroectodermal tumour (PNET), rhabdomyosarcoma (except spindle cell and botyroid types), angiosarcoma, pleomorphic liposarcoma, osteosarcoma (medullary and soft tissue), mesenchymal chondrosarcoma, desmoplastic small round cell tumour, malignant fibrous histiocytoma.
— low-grade: well-differentiated liposarcoma, dermatofibrosarcoma protuberans, well-differentiated chondrosarcoma, angiomatoid malignant fibrous histiocytoma.

Others are allocated a grading score (synovial sarcoma (3), myxoid chondrosarcoma (2)), or are not graded but are potentially metastatic: clear cell sarcoma, alveolar soft part sarcoma, epithelioid sarcoma.

Grading is prognostically useful in spindle cell sarcomas: leiomyosarcoma, fibrosarcoma, malignant peripheral nerve sheath tumour.

Grading (Fèdèration Nationale des Centres de Lutte Contre le Cancer).

	Scores	
Differentiation		
well	1	Sarcoma closely resembling adult mesenchymal tissue, e.g. well-differentiated liposarcoma.
moderate	2	Sarcoma of certain histological type, e.g. myxoid liposarcoma.
poor	3	Embryonal and undifferentiated sarcomas and sarcomas of uncertain type, e.g. synovial sarcoma.
Necrosis		
none	1	
≤50% tumour necrosis	2	
>50% tumour necrosis	3	
Mitoses		
0–9/10 hpf	1	
10–19/10 hpf	2	
≥20/10 hpf	3	
Grade 1 = ≤3		
Grade 2 = 4 or 5		
Grade 3 = ≥6		

HPF, high-power fields (×40 objective).

Up to 75% of sarcomas are high-grade histological type and malignancy.

Histological differentiation or grade can be heterogeneous within a tumour, e.g. juxtaposition of well-differentiated and dedifferentiated chondrosarcoma or liposarcoma. The less differentiated component is chosen for grading purposes.

Preoperative adjuvant therapy can lead to quite extensive necrosis and changes in morphology potentially invalidating grading criteria on the resection specimen. In sarcomas the degree of histological tumour response should be graded from I (no effect identified) to IV (no viable tumour noted) with 90–97% response (III) a target standard of favourable prognostic significance. Note that treatment effects (necrosis or fibrosis) can not be reliably distinguished from spontaneous tumour necrosis or degeneration. A majority of paediatric soft tissue sarcomas are treated chemotherapeutically, while surgical excision is used in most adolescent and adult patients. High-grade tumours benefit from a combination of local surgical control and systemic therapy.

4. EXTENT OF LOCAL TUMOUR SPREAD

Border: pushing/infiltrative—an infiltrative margin is adverse.
Lymphocytic reaction: prominent/sparse.
Lymphatics/vessels/nerves including the proximal limit.
Single/more than one anatomical compartment.

Soft tissue sarcoma

The TNM classification applies to alveolar soft part sarcoma, epithelioid sarcoma, extraskeletal chondro-/osteo-/Ewing's sarcomas/PNET, fibrosarcoma, leiomyosarcoma, liposarcoma, malignant fibrous histiocytoma, malignant haemangiopericytoma, malignant mesenchymoma, malignant peripheral nerve sheath tumour, rhabdomyosarcoma, synovial sarcoma and sarcoma, not otherwise specified. The following are excluded: angiosarcoma, Kaposi's sarcoma, dermatofibrosarcoma protuberans, fibromatosis and sarcomas arising from dura mater, brain, hollow viscera or parenchymatous organs except breast.

pT1 tumour ≤5 cm in greatest dimension
  a. superficial
  b. deep
pT2 tumour >5 cm in greatest dimension
  a. superficial
  b. deep.

Superficial tumour is located exclusively above the superficial fascia. Deep tumour is located either exclusively beneath the superficial fascia or superficial to the fascia with invasion of or through the fascia. Retroperitoneal, mediastinal and pelvic sarcomas are deep.

Stage grouping also incorporates histological grade: localized non-metastatic lesions are stage I (low grade) or II (high grade). Stage III is localized, high-grade pT2b cancers and stage IV metastatic disease of any pT or histological grade.

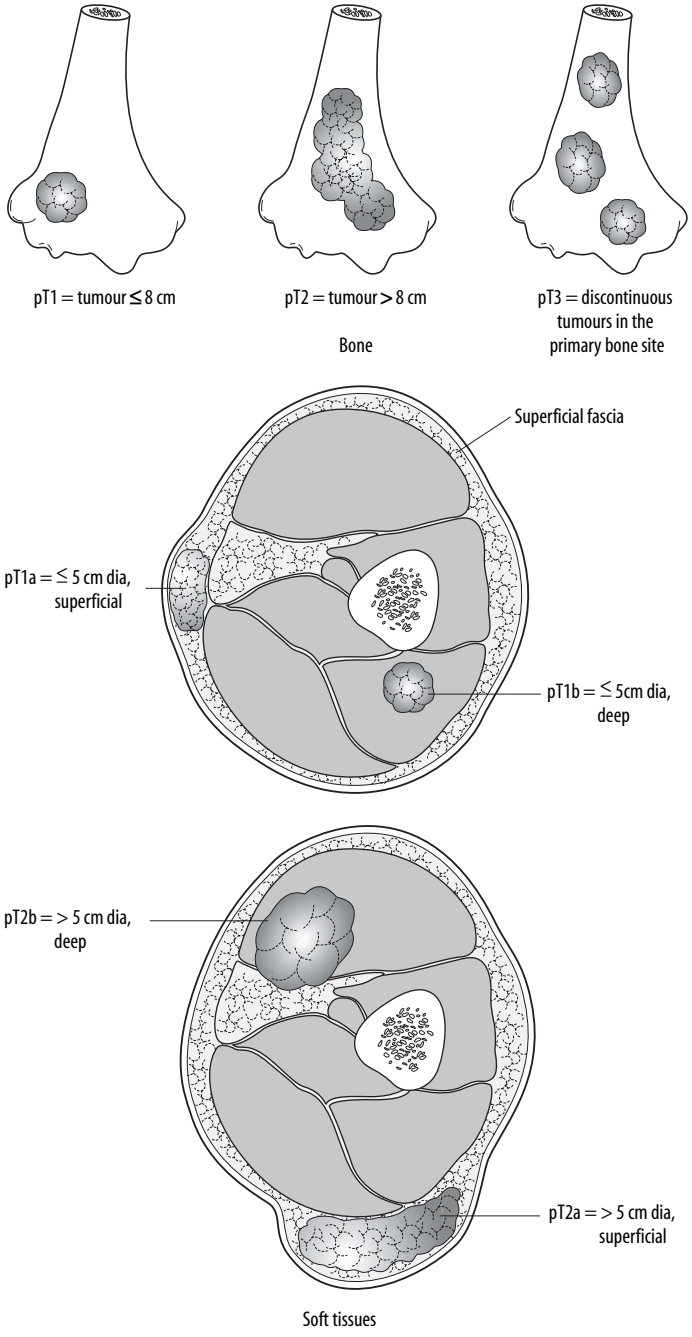


FIGURE 36.1. Sarcoma.

Bone sarcoma

The TNM classification applies to all primary malignant bone tumours except malignant lymphomas, multiple myeloma, surface/juxtacortical osteosarcoma, and juxtacortical chondrosarcoma.

pT1 tumour ≤8 cm in greatest dimension
pT2 tumour >8 cm in greatest dimension
pT3 discontinuous tumours in the primary bone site
pM1a lung metastasis
pM1b other distant sites.

Metastasis in another bone is classified as distant metastasis.

For pT1/pT2 optional descriptors are:

(i) beyond cortex to periosteum
(ii) beyond periosteum to surrounding soft tissues
(iii) with extension to major vessels or nerves.

Stage grouping also incorporates histological grade: localized non-metastatic pT1/pT2 lesions are either stage I (low grade) or II (high grade) and pT3 cancers are stage III (any grade). Stage IV is nodal or metastatic disease of any pT or histological grade. This is somewhat similar to the commonly used Enneking system, stage 3 of which combines TNM stage groups III and IV.

5. LYMPHOVASCULAR INVASION

Present/absent—adverse prognosis when present.
Intra-/extratumoral.

6. LYMPH NODES

Site/number/size/number involved/limit node/extracapsular spread.

Regional nodes: those appropriate to the site of the primary tumour. Regional node involvement is rare and cases in which nodal status is not assessed are considered N0 instead NX.

pN0 no regional lymph node metastasis
pN1 metastasis in regional lymph node(s).

Lymph node metastases are unusual, with the commonest mode of spread being haematogenous resulting in pulmonary secondaries. Some sarcomas, e.g. angiosarcoma, epithelioid sarcoma and synovial sarcoma, may show nodal spread. Alveolar rhabdomyosarcoma can present in lymph nodes or bone marrow as clinical lymphadenopathy or erythroleucocytopaenia mimicking haematological malignancy.

7. EXCISION MARGINS

Distance (mm) to the nearest painted excision margin.

Margins are superficial/deep, proximal/distal, medial/lateral and can be an anatomical structure, e.g. fascia or periosteum. Resection can be intralesional (within the tumour capsule and submitted in fragments), marginal (through the inflammatory tissue surrounding the tumour),

wide (with a cuff of normal tissue) or radical in extent. The latter involves removal of the tumour and its related compartment of soft tissues, with or without the underlying bone, or amputation to include the joint proximal to the tumour. Neoadjuvant chemotherapy with limb salvage surgery is used increasingly for various bone sarcomas.

A surgical margin clearance of less than 15–20 mm in soft tissue sarcoma has an increased risk of local recurrence unless further surgery or radiotherapy is undertaken. This risk may be less if the margin is bound by a fascial plane. For high-grade tumour an ever wider margin (2–5 cm) may be desirable.

8. OTHER PATHOLOGY

Prosthesis allied to limb salvage surgery following wide local excision with preoperative neoadjuvant therapy.

Radio-/chemotherapy changes: necrosis/inflammation and fibrosis in the primary tumour. Similar changes are seen in metastases and also tissue maturation, e.g. pulmonary metastases of osteosarcoma resulting in nodules of paucicellular osteoid.

Paget's disease of bone, childhood chemotherapy and irradiation predispose to osteosarcoma.

FNAC and needle core biopsy of soft tissue masses can allow categorization into benign and malignant lesions in a majority of cases. They can also exclude diagnoses such as metastatic carcinoma, lymphoma and malignant melanoma, allowing a more focused approach to the diagnosis of sarcoma. However, the pathologist must be aware of the potential for sampling error with regard to heterogeneity in tumour type and grade and the latter should only be commented on if it is high grade. The use of preoperative needle biopsy with neoadjuvant treatment can impose limitations on the prognostic information in the resection, e.g. necrosis induced by adjuvant therapy invalidates traditional grading criteria.

Immunophenotype

Immunohistochemical markers can be applied to formalin-fixed paraffin-embedded tissue to demonstrate a range of epithelial, neural, muscular, vascular and other mesenchymal antigens. None is totally specific or sensitive, indicating that an assimilation of results (including negative ones) from a panel of antibodies is necessary. However, for some soft tissue sarcomas a positive immunohistochemical profile is part of the definition of the tumour, e.g. rhabdomyosarcomas, epithelioid sarcoma, clear cell sarcoma, desmoplastic small round cell tumour and gastrointestinal stromal tumours. It is also of use in diagnosing synovial sarcomas and malignant vascular tumours.

Antibody	Use
Cytokeratin	Synovial/epithelioid sarcoma
EMA	Synovial/epithelioid sarcoma
Desmin (polyclonal), myo-D1, myogenin	Rhabdomyosarcoma
Desmin, h-caldesmon, smooth muscle actin	Leiomyosarcoma

S100 protein	Malignant peripheral nerve sheath tumour, adipocytic and cartilaginous differentiation, clear cell sarcoma, synovial sarcoma
CD99 (MIC-2), Fli-1	Ewing's sarcoma (plus PAS for glycogen)
Factor VIII, CD31, CD34	Vascular markers (angiosarcoma)
CD34	Dermatofibrosarcoma
HMB-45	Clear cell sarcoma
HHV8 (RT-PCR)	Kaposi's sarcoma
WT1	desmoplastic small round cell tumour (polyimmunophenotypic: also cytokeratins/EMA/desmin).

Chromosomal analysis

Chromosomal analysis is gaining increasing importance in classification, prognosis and choice of treatment for a range of sarcomas, e.g. Ewing's sarcoma, peripheral neuroectodermal tumours, liposarcoma, synovial sarcoma, rhabdomyosarcoma and desmoplastic small round cell tumour. Fresh tissue in a suitable transport medium is required for tissue culture although reverse transcriptase-polymerase chain reaction (RT-PCR) techniques are being developed for use on paraffin-embedded tissue.

Prognosis

Prognosis in soft tissue sarcomas relates to:

— tumour size: >5 cm diameter.
— grade: low vs. high grade.
— stage.
— histological type.
— site: superficial vs. deep extremity vs. retroperitoneum.
— age: >50 years.
— adequacy of surgery.

The importance of excision margins is emphasized in soft tissue sarcomas where negative and positive margins in low-grade lesions are associated with 5-year recurrence rates of 2% and 28%, respectively. Current treatment of soft tissue sarcomas is wide monobloc resection with postoperative adjuvant radiotherapy to the operative site of high-grade lesions. With modern surgical techniques and adjuvant chemo-/radiotherapy average 5-year survival figures for soft tissue and bone-based sarcomas are 70–80%. Prognosis varies with tumour stage, infiltrative margins, vascular invasion, completeness of excision, histological type, e.g. chondrosarcoma is better than osteosarcoma (60%), and grade: grade I chondrosarcoma (78%) vs. grade III (22%), myxoid liposarcoma (75%) vs. round cell (28%), embryonal (botryoid/spindle cell: 85–95%) vs. alveolar (53%) rhabdomyosarcoma. Grade of response to preoperative chemotherapy is also a very important indicator. Surgical excision of pulmonary metastases (20% of sarcomas) is also helpful.

9. OTHER MALIGNANCY

Metastatic carcinoma, malignant melanoma, lymphoma (primary or secondary) and leukaemia can all mimic soft tissue or bone sarcoma and immunohistochemical markers will be required to make these distinctions. Lymphoma is usually of high-grade B-cell type, solitary but occasionally multifocal. The cells are CD45/CD20 positive with large irregular, multilobated nuclei. Fibrosis is present in 50% of cases giving spindle cell (mimicking sarcoma) or compartmentalized (mimicking metastatic carcinoma) appearances. A minority are CD30 positive with cytological features of anaplastic lymphoma and aggressive behaviour. Metastatic carcinoma to bone may be osteolytic (breast, lung, thyroid, renal) leading to pathological fracture or osteoblastic (prostate) in character. It can be focal or diffuse resulting in a leucoerythroblastic blood picture and extramedullary haematopoiesis. Rarely the bone marrow can show a granulomatous response as an indicator of micrometastasis (e.g. infiltrating lobular carcinoma of breast), which can be demonstrated by immunohistochemistry. Certain carcinomas tend to a preferred pattern of bone metastases, e.g. thyroid carcinoma goes to shoulder girdle, skull, ribs and sternum. Metastatic disease is usually to the axial skeleton and rarely to the hands and feet.

Carcinoma
— cytokeratins, CEA, EMA.
Malignant melanoma
— S100, HMB-45, melan-A.
Leukaemia
— CD68, myeloperoxidase, chloroacetate esterase, tdt.
Specific markers
— thyroglobulin/TTF-1 (thyroid), PSA (polyclonal)/PSAP (prostate), CA125 (ovary), ER/PR/GCDFP-15 (breast), PLAP/AFP/βHCG/CD30 (germ cell tumour).

10. COMMENTS ON RETROPERITONEUM

The retroperitoneum contains the kidneys, adrenal glands, ureters, aorta, inferior vena cava, vessel tributaries, lymph nodes, nerve plexuses and autonomic ganglia. Due to its inaccessible anatomical location tumours can attain a considerable size before clinical presentation with vague symptomatology or because of pressure effects on adjacent structures, e.g. ureter. Investigation is by CT scan supplemented by ultrasound and MRI as appropriate. Arteriography may be used if resection of a large tumour is planned. Tissue diagnosis is by percutaneous CT-guided needle core biopsy or FNA. The commonest malignancy by far is periaortic lymphadenopathy due to nodal malignant lymphoma (diffuse large B-cell or follicular lymphoma) or metastatic disease (testicular germ cell tumour, gut, prostate, renal, pancreatic or gynaecological cancer). The need for a tissue diagnosis is determined by the availability of previous data, the nature and stage of the disease process at which the lymphadenopathy has arisen and any further planned therapeutic management, e.g. frozen section as a prequel to radical gynaecological resection, needle core

biopsy to establish a diagnosis of malignant lymphoma, or imaging with serum tumour markers to indicate surgery or radio-/chemotherapy in a patient with known previous testicular germ cell tumour. Kidney, germ cell and adrenal gland tumours are dealt with in their respective sections but primary tumours include:

Liposarcoma: especially well-differentiated and sclerosing subtypes. May contain a dedifferentiated element.

Leiomyosarcoma: arising from the wall of the inferior vena cava or its tributaries and prone to cystic change when large. Tumour necrosis and size >10 cm are strong pointers to malignancy even if of low mitotic rate.

Malignant fibrous histiocytoma: exclude this pattern as part of other sarcomas and also sarcomatoid renal carcinoma.

Peripheral nerve tumours: neurilemmoma, neurofibroma, malignant peripheral nerve sheath tumours, paraganglioma, ganglioneuroma, neuroblastoma.

Ewing's sarcoma/PNET, rhabdomyosarcoma, desmoplastic small round cell tumour: usually in children and young adults and initial chemotherapy is more appropriate, but may be supplemented by surgery which is the main modality in the other sarcoma types.

Resection specimens can be large and complex with structures such as kidney enveloped by tumour. For TNM staging purposes retroperitoneum is a deep structure. Due to the late presentation and difficulties in obtaining complete excision, prognosis for soft tissue sarcomas is poor with an overall 5-year survival of about 25%.

11. COMMENTS ON ADRENAL GLAND

Metastatic carcinoma in the adrenal gland, particularly from lung, breast and kidney, is commoner than a primary neoplasm and usually detected by follow-up CT scan. Sometimes CT-guided needle core biopsy or FNA is used to make this distinction and more often primary adrenal neoplasms present either as a symptomatic or incidental mass or are characterized by their endo-crinological symptoms and signs and resultant biochemical profiles. Phaeochromocytoma is a contraindication to biopsy due to the risk of a catecholamine-induced hypertensive crisis. CT/MRI scans can assess the size, characteristics and bilaterality of adrenal lesions, helping to distinguish hyperplasia (secondary to hyperpituitarism and usually bilateral) from neoplasm but are poor at designating benignity from malignancy apart from on the basis of size. Adrenal carcinoma cells are often dysfunctional and the tumour reaches a significant size (most are >5 cm/50–100 g) before presentation. Histologically the best indicators of malignancy are mitoses (>5 cm/50 hpfs), diffuse growth pattern, necrosis, fibrous bands, capsular and vascular invasion. However, it can be difficult to distinguish an adenoma from a well-differentiated adrenocortical carcinoma and the term adrenocortical neoplasm may be used qualified by a morphological assessment of its likelihood to recur. Spread is to lymph nodes, liver and lung, sometimes with local invasion

into kidney and inferior vena cava. Treatment is aimed at complete local excision, which may be laparoscopic for small lesions but an open thoracoabdominal approach for a larger tumour. Overall 5-year survival for adrenal carcinoma is 35%. Characteristic hormonal effects of adrenal cortical tumours are hypercortisolism (Cushing's syndrome), hyperaldosteronism (Conn's syndrome) and virilization.

Phaeochromocytoma is medullary in location, 3–5 cm in diameter and 75–150 g in weight, or larger, with a pale to tan coloured cut surface. It is associated with MEN2A/2B, von Hippel Lindau disease and neurofibromatosis. Similar extra-adrenal paragangliomas are found elsewhere along sympathetic/parasympathetic nervous system sites in the retroperitoneum, mediastinum, carotid body, middle ear and urinary bladder with variable secretory capacity and functionality, e.g. chemodectomatous head and neck paragangliomas. Adrenal phaeochromocytoma has a characteristic nested "Zellballen" pattern its cells secreting catecholamines and inducing paroxysmal symptoms of flushing, sweating, tachycardia, tremor and hypertension. Surgical excision requires careful control of blood pressure to avoid a hypertensive crisis. Overall survival is 50% with 10% bilateral or extra-adrenal or malignant. Malignant behaviour cannot be predicted histologically, with metastases being the only reliable criterion. Spread is usually to lymph nodes, then the axial skeleton, liver, lung and kidney.

Neuroblastoma and ganglioneuroblastoma are characteristically seen in infants and children and are not further considered.

Immunophenotype of adrenal neoplasms

— adrenal carcinoma: positive for cytokeratins (variable), vimentin, synaptophysin, inhibin, melan-A. CEA negative. Strong positivity for cytokeratin, EMA and CD10 would favour metastatic renal clear cell carcinoma, one of its main differential diagnoses.
— phaeochromocytoma: positive for catecholamines, chromogranin, synaptophysin, neurofilament, cytokeratins (±) and intervening S100 positive sustentacular cells.

TMN stage of adrenal cortical carcinoma: a proposed scheme is

pT1 tumour confined to adrenal gland and ≤5cm in greatest dimension
pT2 tumour confined to adrenal gland and >5 cm in greatest dimension
pT3 tumour of any size, locally invasive but not involving adjacent organs
pT4 tumour of any size with invasion of adjacent organs
pN0 no regional lymph node metastasis
pN1 metastasis in regional lymph node(s).

Other adrenal malignancy includes malignant lymphoma and melanoma usually secondary to disseminated disease. Occasional benign lesions are ganglioneuroma, adrenal cysts, adenomatoid tumour and myelolipoma.

Ophthalmic Cancer

- Intraocular Malignancy
- Extraocular Malignancy

37
Intraocular Malignancy

1. GROSS DESCRIPTION

Specimen

— fine needle aspirate/local resection/evisceration/enucleation/exenteration.
— weight (g).
— anteroposterior, horizontal and vertical dimensions (cm).
  - length of optic nerve (mm)
  - ocular malignancy usually presents as an alteration in visual acuity and is rarely aspirated or biopsied due to potential tumour seeding. Unless small and anteroequatorial when a local resection may be considered, treatment is usually by enucleation (removal of the globe with a short piece of optic nerve) or exenteration if significant extraocular spread is present. Exenteration is more usually reserved for extraocular malignancy, e.g. of eyelids and orbital contents.

Tumour

Site

— bulbar conjunctiva/sclera/cornea: malignant melanoma, lymphoma, squamous carcinoma.
— iris/ciliary body/choroid: uveal melanoma.
— retina/optic nerve: retinoblastoma.
— anterior chamber/posterior chamber: posterior or equatorial—superior, inferior, lateral. Posterior lesions are better prognosis than equatorial as they interfere with visual acuity and present earlier, whereas the latter can attain a larger size with potential for involvement of scleral and Schlemm's canal vessels.

Size

— length × width × depth (mm) but in particular maximum tumour dimension (mm).

Appearance

— nodular/plaque/diffuse/multicentric/pigmented/non-pigmented/haemorrhage/necrosis/calcification.

Edge
— circumscribed/irregular.

2. HISTOLOGICAL TYPE

Malignant melanoma
— 80% in the choroid and the commonest intraocular malignancy in adults. It elevates and detaches the overlying retina.

Retinoblastoma
— <3 years of age and 40% familial, of which 90% are bilateral; retinoblastoma suppressor gene (Rb) 13q14 deletion.

Metastatic carcinoma
— breast, lung, gastrointestinal tract (stomach).
— 10% incidence at autopsy in carcinomatosis.
— posterior choroid is the commonest site.

Leukaemia/lymphoma
— 50% of leukaemia patients at autopsy (infiltration and/or haemorrhage).
— lymphoma is usually secondary to extraocular disease.

Rare
— medulloepithelioma, glioma, meningioma of optic nerve.

3. DIFFERENTIATION

Malignant melanoma
— spindle cell better prognosis
  • slender cells, indistinct nucleolus, longitudinal fold in the nuclear membrane (spindle cell type A)
  • nucleolar enlargement (spindle cell type B) is an adverse prognostic sign.
— epithelioid cell worse prognosis.
— mixed (50%).
— S100, HMB-45, melan-A positive, ± CAM5.2.

Retinoblastoma
— small round cells with basophilic nuclei and scant cytoplasm, calcification, mitoses and Homer Wright rosettes.
— well differentiated: fleurettes and Flexner-Wintersteiner rosettes.
— poorly differentiated: vascular pseudo-palisading necrosis, mitoses, apoptosis, absence of rosettes.
— S100, NSE, synaptophysin, GFAP positive, high Ki-67 index.

4. EXTENT OF LOCAL TUMOUR SPREAD
Border: pushing/infiltrative.
Lymphocytic reaction: prominent/sparse.

Intraocular: ciliary body, iris, anterior chamber.
Transscleral/extrascleral spread: depth (mm).
Optic nerve invasion.

Uveal melanoma of choroid and ciliary body

pT1 ≤10 mm basal diameter, ≤2.5 mm apical height
- a. without extraocular extension
- b. with microscopic extraocular extension
- c. with macroscopic extraocular extension

pT2 >10 to 16 mm basal diameter, >2.5 to 10 mm apical height
- a. without extraocular extension
- b. with microscopic extraocular extension
- c. with macroscopic extraocular extension

pT3 >16 mm basal diameter and/or >10 mm apical height without extraocular extension

pT4 >16 mm basal diameter and/or >10 mm apical height with extraocular extension.

When basal diameter and apical height show a difference in classification, use the highest category. Extraocular extension is diagnosed if the tumour grows outside the bulb with invasion of the orbit (commonest), optic nerve, outer eye muscles, lacrimal apparatus or conjunctiva.

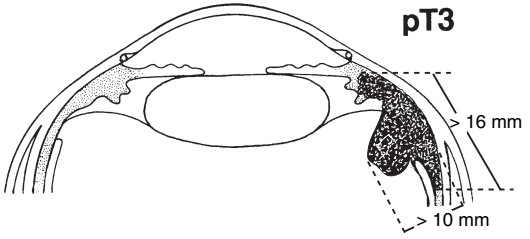


FIGURE 37.1. Malignant melanoma of choroid.

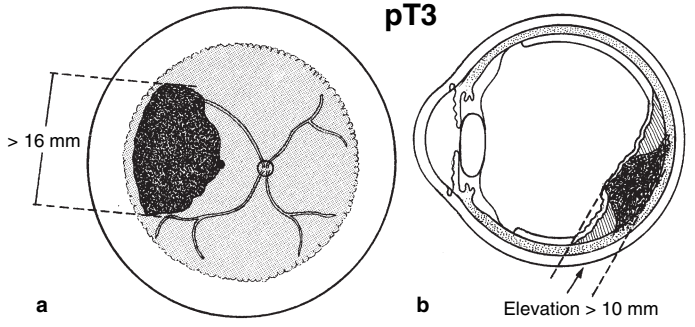


FIGURE 37.2. Malignant melanoma of choroid.

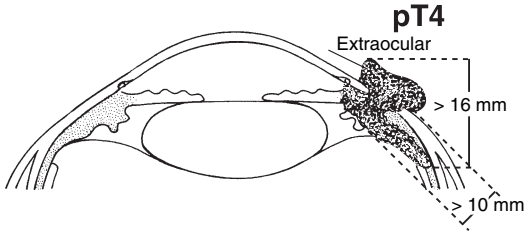


FIGURE 37.3. Malignant melanoma of choroid.

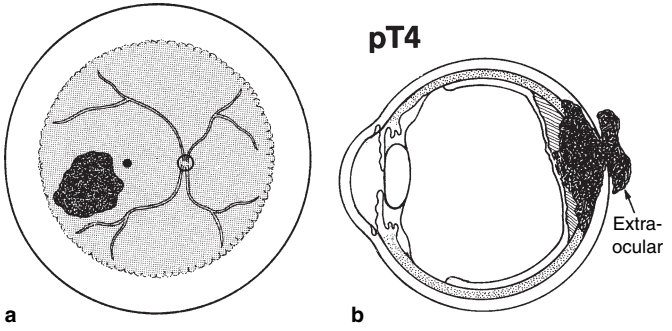


FIGURE 37.4. Malignant melanoma of choroid.

There is a tendency for spread along the optic nerve with metastases to liver, lung, bone and skin.

Retinoblastoma

— in bilateral cases the eyes are classified separately. The classification does not apply to complete spontaneous regression of the tumour.
— endophytic, exophytic (subretinal) or retinal spread.

pT1 tumour confined to retina, vitreous, or subretinal space. No optic nerve or choroidal invasion

pT2 minimal invasion of optic nerve or optic coats or focal invasion of choroid
- a. tumour invades optic nerve up to, but not through, the level of lamina cribrosa
- b. tumour invades choroid focally
- c. tumour invades optic nerve up to, but not through, the level of lamina cribrosa and invades choroid focally

pT3 significant invasion of optic nerve or optic coats or massive invasion of choroid
- a. tumour invades optic nerve through the level of lamina cribrosa but not to line of resection

b. tumour massively invades the choroid
c. tumour invades optic nerve through the level of lamina cribrosa but not to the line of resection and massively invades choroid.

pT4 extraocular extension which includes any of the following:
- invasion of optic nerve to the line of resection
- invasion of orbit through sclera
- extension both anteriorly or posteriorly into orbit
- extension into brain
- extension into subarachnoidal space of optic nerve
- extension to apex of orbit
- extension to, but not through, chiasm
- extension into brain beyond chiasm.

There is a tendency for spread along the optic nerve into subarachnoid fluid and brain with metastases to the cranial vault and skeleton (pM1: bone marrow).

5. LYMPHOVASCULAR INVASION

Present/absent.
Intra-/extratumoral.
Schlemm's canal of ciliary body to the conjunctival veins.
Vortex veins via the sclera: adverse prognostic sign.

6. LYMPH NODES

Site/number/size/number involved/limit node/extracapsular spread.
Regional nodes: pre-auricular, submandibular, cervical.

pN0 no regional lymph node metastasis
pN1 metastasis in regional lymph node(s).

7. EXCISION MARGINS

Distances (mm) to the nearest painted resection margin of the optic nerve or edge of the exenteration.

8. OTHER PATHOLOGY

Tumour necrosis
— spontaneous or secondary to aspiration cytology or irradiation/cryotherapy/photocoagulation.

Glaucoma
— invasion of Schlemm's canal or secondary to aspiration cytology.

Metastatic malignant melanoma
— jaundice, hepatomegaly due to secondary deposits and a glass eye.

Prognosis

Malignant melanoma has a 15-year mortality rate of 50%, but 66% at 5 years for those with extrascleral extension. Maximum tumour dimen-

sion is the strongest prognostic indicator. Cell type is influential as 5-year survival rates are lower in epithelioid (25–35%) than spindle cell B lesions (66–75%). Therefore a small (<7 mm) pure spindle cell A melanoma has a 5-year survival ≥95%. Retinoblastoma has a 5-year survival of 90%. The hereditary form is slightly worse and 6–20% of patients develop a second malignancy after 10–15 years, e.g. osteosarcoma, rhabdomyosarcoma. Localized resection of malignant melanoma may be considered if it is small (maximum dimension <1 cm) and anterior or equatorial in location. Enucleation is indicated for posterior melanoma, irrespective of its size, due to its interference with visual acuity. Sporadic retinoblastoma is treated by enucleation (unless early, when radiation is used) and familial cases by enucleation and selective radiotherapy to the contralateral eye to treat any early metachronous lesions. Irradiation and systemic chemotherapy are reserved for cases with involvement of the surgical margins.

Adverse prognostic indicators in malignant melanoma are:

— tumour maximum dimension with small, medium and large tumours approximating to pT1, pT2 and pT3.
— epithelioid cell type/nucleolar enlargement.
— invasion of the ciliary body, anterior chamber, optic nerve, sclera, vortex veins and extraocular extension.
— necrosis, mitotic activity, tumoral and extratumoral vascular invasion.

Adverse prognostic indicators in retinoblastoma are:

— invasion of optic nerve, particularly its surgical margin.
— invasion of sclera, choroid, anterior segment.
— tumour size, multifocality and differentiation.

38
Extraocular Malignancy

1. GROSS DESCRIPTION

Specimen

— fine needle aspirate/excision biopsy/exenteration.

- size (cm) and weight (g).
- extraocular tumours can present as an obvious nodule or plaque (eyelid, conjunctiva), swelling (lacrimal apparatus), proptosis or exophthalmos (orbital). Tissue diagnosis and treatment of eyelid and conjunctiva lesions usually involves primary local excision sufficient to remove the tumour but minimized to preserve function. Excision is by wedge (eyelid) or strip (conjunctiva) resection and these oculoplastic procedures may sometimes require intraoperative frozen section assessment of surgical margins. Exenteration is reserved for those tumours showing more extensive local spread demonstrated by CT or MRI scans. Pleomorphic adenoma of the lacrimal gland is usually amenable to local excision via a lateral orbitotomy but like adenoid cystic carcinoma may require more extensive surgery. Initial investigation of orbital tumours dictates planned management with avoidance of surgical excision of irresectable primary malignancies and metastatic tumours. Tissue diagnosis may be obtained by FNA or punch biopsy but often the latter is insufficient and a formal, deep, open biopsy via a lateral orbitotomy is required. Clinical assessment should consider various non-surgical possibilities, e.g. metastatic carcinoma, malignant lymphoma, thyrotoxicosis and Wegener's granulomatosis. Surgery is geared towards excision of localized primary tumours, e.g. cavernous haemangioma, pleomorphic adenoma, but exenteration, involving removal of the eye, surrounding orbital contents, eyelids, nasolacrimal apparatus ± orbital bone, may be required. The commonest indications for exenteration are malignant tumours of the eyelid such as basal cell, squamous cell or sebaceous carcinomas.

Tumour

Site
— ocular adnexae: eyelid
conjunctiva
lacrimal apparatus.
— orbit/retro-orbital tissues.

Size
— length × width × depth (cm) or maximum dimension (cm).

Appearance
— exophytic/verrucous/sessile/ulcerated/fleshy/infiltrative/pigmented.

Edge
— circumscribed/irregular.

2. HISTOLOGICAL TYPE

Adnexae
— basal cell carcinoma: most common, >80%.
— squamous cell carcinoma: 5–10%.
— sebaceous carcinoma: epithelioma/carcinoma.
— Merkel cell carcinoma: NSE/chromogranin/synaptophysin/cytokeratin (CAM5.2, CK20) positive; aggressive.
— malignant melanoma: primary (de novo or origin in eyelid/conjunctional naevus, or acquired conjunctival melanosis) or secondary.
— lymphoma: low-grade MALToma with indolent behaviour.
— metastatic carcinoma: breast, gut, lung.
— lacrimal gland tumours: e.g. pleomorphic adenoma, adenoid cystic carcinoma and other salivary type neoplasms.

Orbit: children
— embryonal (less commonly alveolar) rhabdomyosarcoma, Burkitt's lymphoma.

Orbit: adults
— haemangioma, neurilemmoma, lipoma, nodular fascitis, Langerhans cell histiocytosis.
— inflammatory pseudotumour: 20–40 years of sudden onset and painful but potentially steroid responsive.
— lymphoma (MALToma): the presence of lymphoid tissue in the orbit (not usual) is suspicious of neoplasia and up to 50% are part of systemic disease.
— haemangiopericytoma.
— fibro-/osteo-/chondro-/liposarcoma, malignant fibrous histiocytoma, alveolar soft part sarcoma, malignant teratoma are all rare, but

fibrosarcoma/malignant fibrous histiocytoma is the commonest orbital sarcoma of adulthood. There is an overlap with solitary fibrous tumour.

— glioma or meningioma of optic nerve origin.
— myeloma/leukaemia.
— metastatic carcinoma
  15–30% of orbital tumours
  direct spread: retinoblastoma; uveal melanoma; paranasal sinus carcinoma
  distant spread: neuroblastoma; embryonal rhabdomyosarcoma; breast, lung, kidney, prostatic carcinoma, carcinoid tumour of lung or small bowel.
— malignant melanoma: direct or distant spread.

3. DIFFERENTIATION

Well/moderate/poor/undifferentiated, or Grade 1/2/3/4.

— carcinoma.

Low-grade/high-grade.

— lymphoma and sarcoma.

4. EXTENT OF LOCAL TUMOUR SPREAD

Border: pushing/infiltrative.
Lymphocytic reaction: prominent/sparse.
The TNM classification varies according to exact anatomical site and tumour type.

Adnexae, e.g. carcinoma of eyelid. Malignant melanoma is classified as for skin tumours

pT1 tumour of any size not in tarsal plate, or at lid margin ≤5 mm maximum dimension
pT2 tumour invades tarsal plate, or at lid margin >5 mm but ≤10 mm maximum dimension
pT3 tumour involves full eyelid thickness, or at lid margin >10 mm maximum dimension
pT4 tumour invades adjacent structures which include bulbar conjunctiva, sclera/globe, soft tissues of orbit, perineural invasion, bone/periosteum of orbit, nasal cavity/paranasal sinuses, and central nervous system.

Orbit

The TNM classification applies to sarcomas of soft tissues and bone.

pT1 tumour ≤15 mm maximum dimension
pT2 tumour >15 mm maximum dimension without invasion of globe or bony wall

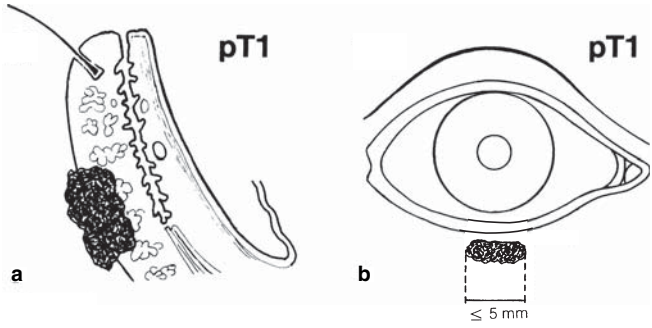


FIGURE 38.1. Eyelid carcinoma.

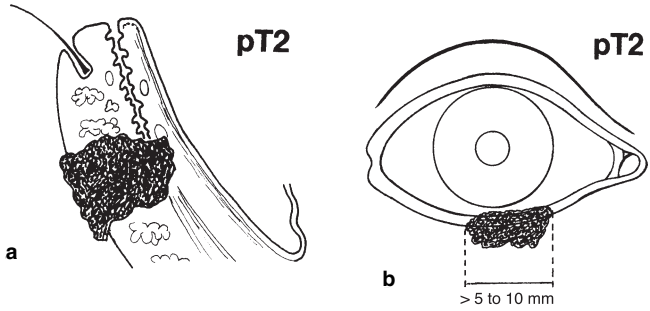


FIGURE 38.2. Eyelid carcinoma.

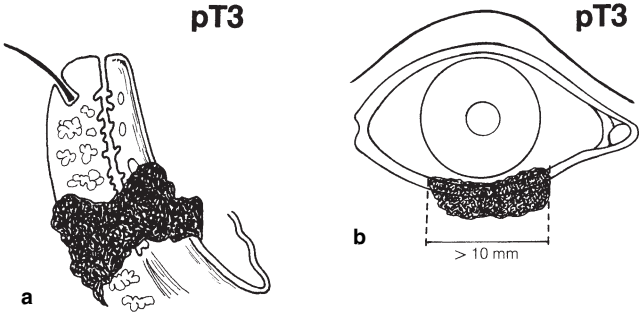


FIGURE 38.3. Eyelid carcinoma.

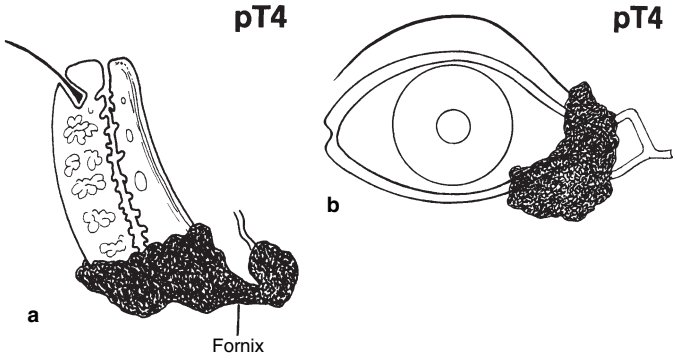


FIGURE 38.4. Eyelid carcinoma.

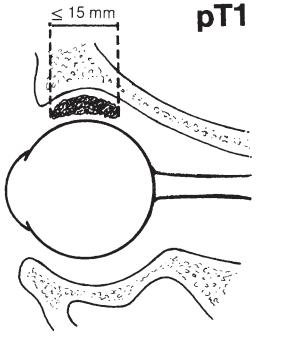


FIGURE 38.5. Sarcoma of orbit.

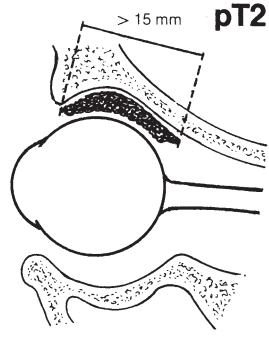


FIGURE 38.6. Sarcoma of orbit.

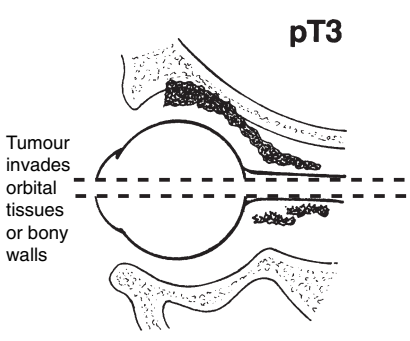


FIGURE 38.7. Sarcoma of orbit.

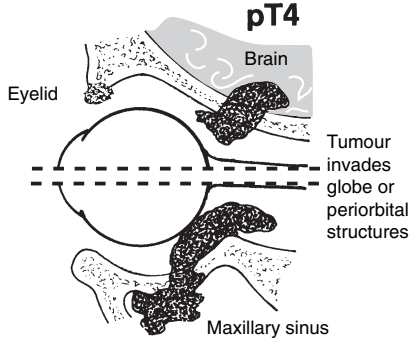


FIGURE 38.8. Sarcoma of orbit.

pT3 tumour of any size with invasion of orbital tissues and/or bony walls
pT4 tumour invades globe or periorbital structures such as: eyelids, temporal fossa, nasal cavity/paranasal sinuses, or central nervous system.

5. LYMPHOVASCULAR INVASION
Present/absent.
Intra-/extratumoral.

6. LYMPH NODES
Site/number/size/number involved/limit node/extracapsular spread.
Regional nodes: pre-auricular, submandibular, cervical.

pN0 no regional lymph node metastasis
pN1 metastasis in regional lymph node(s).

7. EXCISION MARGINS
Distances (mm) to the nearest painted excision margins.

8. OTHER PATHOLOGY
Mikulicz's disease (the pathology of which is similar to Sjögren's syndrome) is characterized by benign lymphoepithelial lesion (syn. lympho(myo-)epithelial sialadenitis) and in 10–15% progresses to develop low-grade lymphoma of MALT type.

Sun exposure, actinic keratosis and Bowen's disease are predisposing factors in carcinoma of the eyelid and conjunctiva.

Prognosis
Orbital tumours present with unilateral proptosis, the commonest types being malignant lymphoma and metastatic carcinoma. Rhabdomyosarcoma occurs in childhood, embryonal variants being of better prognosis than the alveolar type. A 50% survival is achieved with chemo-/radiotherapy and resection is reserved for non-responsive cases. Malignant fibrosarcoma/fibrous histiocytoma is the commonest type of sarcoma in adulthood, with aggressive cases showing a 10-year survival rate of 20–25%. It is treated by radiotherapy. Note that an orbital tumour may be the first presentation of an ocular tumour due to direct spread, e.g. retinoblastoma or malignant melanoma.

The tissues behind the orbital septum are normally devoid of lymphatics and lymphoid tissue. The presence of any lymphoid tissue at this site is therefore suspicious of malignancy. Prognosis, which can be unpredictable, relates to the grade and stage of disease but is generally reasonably good (80% survival). Malignant lymphoma is the commonest adult orbital malignancy. Tissues anterior to the septum show a wider range of antigen-driven reactive and low-grade neoplastic lymphoid proliferation. Treatment of malignant lymphoma is radio-/chemotherapy depending on the stage and grade of disease.

Immunophenotype

— malignant melanoma: S100, HMB-45, melan-A.
— malignant lymphoma: CD45, CD20, CD3; κ/λ light chain restriction; heavy/light chain immunoglobulin and T-cell receptor gene rearrangements.
— carcinoma: cytokeratins, EMA (NB plasma cells can also be EMA positive).
— rhabdomyosarcoma: desmin, myogenin, myo D1.

Bibliography

TUMOUR REPORT PROTOCOLS

Association of Directors of Anatomic and Surgical Pathology

- guidelines: http://www.panix.com/~adasp/tumour.htm
- checklists: http://www.panix.com/~adasp/checklist%20page.htm
- cancer sites: adrenal, ampullary, anus, bone, brain and spinal cord, breast, cervix, colon, endometrium, extrahepatic bile ducts, extra-adrenal paragangliomas, eye, and adnexa, fallopian tube, gall bladder, gestational trophoblastic disease, larynx, lip/oral cavity/oropharynx, liver, lung, lymphoma, nose and paranasal sinuses, oesophagus, ovary, pancreas, penis, pleural mesothelioma, prostate, renal pelvis and ureter, renal neoplasms of tubular origin (excluding paediatric renal tumours), salivary gland, skin-carcinoma, skin-melanoma, small bowel, soft tissue, stomach, testis, thyroid, parathyroid, urinary bladder, vagina, vulva.

College of American Pathologists

- full protocols/checklists: http://www.cap.org/apps/docs/cancer_protocols/protocols_index.html
- cancer sites: breast, brain/spinal cord, ampulla of Vater, anus, colon and rectum, oesophagus, extrahepatic bile ducts, gall bladder, liver (including intrahepatic bile ducts), pancreas (endocrine), pancreas (exocrine), small intestine, stomach, kidney, prostate gland, testis, urinary bladder/renal pelvis/ureter, endometrium, fallopian tube, ovary, trophoblastic tumours, uterine cervix, vagina, vulva, thyroid gland, upper aerodigestive tract (including salivary glands), bone marrow, gastrointestinal lymphomas, Hodgkin's lymphoma, Non-Hodgkin's lymphoma, retinoblastoma, uveal melanoma, rhabdomyosarcoma, Wilm's tumour, carcinoma of the skin, melanoma of the skin, heart, lung, thoracic mesothelium, thymoma, adrenal gland, peritoneum.

The Royal College of Pathologists

- standards and datasets for reporting cancers: http://rcpath.org/index.asp?pageID=254
- cancer sites: adrenal cortical/malignant phaeochromocytoma/paraganglioma, adult renal, bladder, breast, central nervous system, cervical, colorectal, endometrial, gastric, head and neck carcinoma and salivary

gland neoplasms, lung, lymphoma, oesophageal, ovarian tumours and fallopian tube and primary peritoneal carcinoma, pancreas, parathyroid, prostate, skin, testicular, thyroid, vulval.

GENERAL

Allen DC. The W5, how and what next of BMS specimen dissection. Curr Diagn Pathol 2004; 10: 429–434.

Allen DC, Cameron RI (eds). Histopathology Specimens. Clinical, Pathological and Laboratory Aspects. Springer. London 2004.

Baak JPA, Janssen E. Morphology and DNA cytometry: reproducibility conditions and clinical outcomes. Histopathology 2004; 44: 603–614.

Buda A, Ockenden NF, Pignatelli M. Microsatellite instability and neoplasia. In Lowe DG, Underwood JCE (eds). Recent Advances in Histopathology. 20. RSM Press. London 2003; 167–184.

Chetty R, O'Leary JJ, Gatter KC. Immunocytochemistry as a diagnostic tool. Curr Diagn Pathol 1995; 2: 38–45.

Chu PG, Weiss LM. Keratin expression in human tissues and neoplasms. Histopathology 2002; 40: 403–439.

Connolly JL, Fletcher CDM. What is needed to satisfy the American College of Surgeons Commission on Cancer (COC) requirements for the pathologic reporting of cancer specimens? Hum Pathol 2003; 34: 111.

Cross SS. Grading and scoring in histopathology. Histopathology 1998; 33: 99–106.

Cross SS. The molecular pathology of new anti-cancer agents. Curr Diagn Pathol 2005; 11: 329–339.

DeLellis RA, Lloyd RV, Heitz PU, Eng C (eds). World Health Organisation Classification of Tumours. Pathology and Genetics. Tumours of Endocrine Organs. IARC Press. Lyon 2004.

Dey P. Aneuploidy and malignancy: an unsolved equation. J Clin Pathol 2004; 57: 1245–1249.

Domizio P, Lowe D. Reporting histopathology sections. Chapman and Hall. London. 1997.

Du Boulay C. Error trapping and error avoidance in histopathology. In: Lowe DG, Underwood JCE (eds). Recent Advances in Histopathology. 20. RSM Press. London 2003; 103–114.

Expert Advisory Group on Cancer to the Chief Medical Officers of England and Wales. A policy framework for commissioning cancer services. London: Department of Health, 1995 (EL (95) 51).

Eyden B. Electron microscopy in tumour diagnosis: continuing to complement other diagnostic techniques. Histopathology 1999; 35: 102–108.

Fletcher CDM (ed). Diagnostic histopathology of tumours. 2nd edn. Churchill Livingstone. London 2000.

Fletcher JA. DNA in situ hybridization as an adjunct in tumor diagnosis. Am J Clin Pathol 1999; 112(Suppl 1): S11–S18.

Furness P. Developing and running an EQA scheme in diagnostic histopathology. Curr Diagn Pathol 2004; 10: 435–443.

Geradts J. Immunohistochemical prognostic and predictive markers in common tumours. CPD Bulletin Cellular Pathology 1999; 1(4): 144–148.

Gray W, McKee GT. Diagnostic Cytopathology. 2nd edn. Churchill Livingstone. London 2003.

Greene FL, Page DL, Fleming ID, Fritz AG, Balch CM, Haller DG, Morrow M (eds). AJCC Cancer Staging Handbook. From the AJCC Cancer Staging Manual. 6th edition. Springer 2002.

Hall PA. DNA ploidy studies in pathology—a critical appraisal. Histopathology 2004; 44: 614–620.
Hammar SP. Metastatic adenocarcinoma of unknown primary origin. Hum Pathol 1998; 29: 1393–1402.
Herrington CS. Demystified . . . in-situ hybridisation. Mol Pathol 1998; 51: 8–13.
Human tissue and biological samples for use in research: operational and ethical guidelines. Medical Research Council. London, 2001. http://mrc.ac.uk/pdf-tissue_guide_fin.pdf
Immunoquery at http://www.ipox.org/login/cfm
Jansani B, Rhodes A. The role and mechanism of high-temperature antigen retrieval in diagnostic pathology. Curr Diagn Pathol 2001; 7: 153–160.
Kirkham N, Lemoine NR (eds). Progress in Pathology. Volume 5. Greenwich Medical Media. London 2001.
Lester SC. Manual of surgical pathology. 2nd edn. Philadelphia. Elsevier Churchill Livingstone 2006.
Liefers GJ, Tollenaar RAEM, Cleton-Jansen AM. Molecular detection of minimal residual disease in colorectal and breast cancer. Histopathology 1999; 34: 385–390.
Lowe DG, Underwood JCE (eds). Recent Advances in Histopathology. 20. RSM Press. London 2003.
Lundin M, Lundin J, Isola J. Virtual microscopy. J Clin Pathol 2004; 57: 1250–1251.
McKay B. Electron microscopy in tumour diagnosis. In: Fletcher CDM (ed). Diagnostic Histopathology of Tumours. Volume 2, 2nd edn. Churchill Livingstone. London 2000; 1785–1823.
McKee PH, Chinyama CN, Whimster W, Bogomoletz WV, Delides GS, de Wolf CJM (eds). Comprehensive Tumour Technology Handbook. UICC. Wiley-Liss. New York 2001.
McNicol AM, Richmond JA. Optimising immunohistochemistry: antigen retrieval and signal amplification. Histopathology 1998; 2: 97–103.
Mills SE, Carter D, Greenson JK, Oberman HA, Reuter V, Stoler MH. Sternberg's Diagnostic Surgical Pathology. 4th edition. Lippincott, Williams and Wilkins. Philadelphia 2004.
Millward EJ, Heatley MK. Cytokeratin immunoassaying profiles in diagnostic pathology. In: Lowe DG, Underwood JCE (eds). Recent Advances in Histopathology. 20. RSM Press. London 2003; 17–28.
O'Leary JJ, Engels K, Dada MA. The polymerase chain reaction in pathology. J Clin Pathol 1997; 50: 805–810.
Orell SR, Sterrett GF, Watters MN-I, Whitaker D. Manual and Atlas of Fine Needle Aspiration Cytology, 3rd edition. Churchill Livingstone. London 1999.
Peale Jr FV, Hillan KJ. Tissue arrays: construction and application. In: Lowe DG, Underwood JCE (eds). Recent Advances in Histopathology. 20. RSM Press. London 2003, 89–102.
Pecciarini L, Cangi M, Doglioni C. Identifying the primary sites of metastatic carcinoma: the increasing role of immunohistochemistry. Curr Diagn Pathol 2001; 7: 168–175.
Rosai J. Rosai and Ackerman's Surgical Pathology. 9th edition. Mosby. Toronto 2004.
Roskell DE, Buley ID. Fine needle aspiration cytology in cancer diagnosis. Is quick, cheap and accurate when used appropriately. BMJ 2004; 329: 244–245.
Silverberg SG, DeLellis RA, Frable WJ, Li Volsi VA, Wick MR (eds). Silverberg's Principles and Practice of Surgical Pathology and Cytopathology. 4th edition. Churchill Livingstone Elsevier. Philadelphia 2006.

Sobin LH, Wittekind Ch (eds). TNM Classification of malignant tumours. 6th edn. UICC. Wiley-Liss. New York 2002.
Spence RAJ, Johnston G (eds). Oncology. Oxford University Press. Oxford 2001.
Sternberg SS (ed). Histology for Pathologists. 2nd edn. Lippincott-Raven. Philadelphia 1997.
Troxel DB. Error in surgical pathology. Am J Surg Pathol 2004; 28: 1092–1095.
Van den Rijn M, Gilks CB. Applications of microarrays to histopathology. Histopathology 2004; 44: 97–108.
Westra WH, Hruban RH, Phelps TH, Isacson C. Surgical Pathology Dissection. An Illustrated Guide. 2nd edn. Springer. New York 2003.
Wittekind CH, Greene FL, Henson DE, Hutter RVP, Sobin LH. TNM Supplement. A Commentary on Uniform Use, 3rd edn. UICC. Wiley-Liss. New York 2003.
Wittekind C, Greene FL, Hutter RVP, Klimpfinger M, Sobin LH. TNM Atlas 5th edn. Illustrated Guide to the TNM/pTNM Classification of Malignant Tumours. UICC. Springer 2004.
Williams GR. Unravelling the unknown primary. CPD Bulletin Cellular Pathology 1999; 1(4): 140–143.

GASTROINTESTINAL CANCER

General

Capella C, Heitz PU, Höfler H, Solcia E, Klöppel G. Revised classification of neuroendocrine tumours of the lung, pancreas and gut. Virchows Arch 1995; 425: 547–560.
Day DW, Jass JR, Price AB, Shepherd NA, Sloan JM, Talbot IC, Warren BF, Williams GT. Morson and Dawson's Gastrointestinal Pathology, 4th edn. Blackwell Science. Oxford 2005.
Fenoglio-Preiser CM, Noffsinger AE, Stemmermann GN, Lautz PE, Listrom MB, Rilke FO. Gastrointestinal Pathology. An Atlas and Text, 2nd edn. Lippincott Williams and Wilkins. Philadelphia 1999.
Goldman H. Gastrointestinal mucosal biopsy. Churchill Livingstone. New York 1996.
Grabsch H, Kerr D, Quirke P. Is there a case for routine clinical application of ploidy measurements in gastrointestinal tumours? Histopathology 2004; 45: 312–334.
Hamilton SR, Aaltonen LA (eds). World Health Organisation Classification of Tumours. Pathology and Genetics. Tumours of the Digestive System. IARC Press. Lyon 2000.
Ming SC, Goldman H (eds). Pathology of the Gastrointestinal Tract, 2nd edn. Williams and Wilkins. Baltimore 1998.
Odze RD, Goldbum JR, Crawford JM. Surgical Pathology of the GI Tract, Liver, Biliary Tract and Pancreas. Saunders. Philadelphia 2004.
Riddell RH, Iwafuchi M. Problems arising from Eastern and Western classification systems for gastrointestinal dysplasia and carcinoma: are they resolvable. Histopathology 1998; 33: 197–202.
Schlemper RJ, Riddell RH, Kato Y et al. The Vienna classification of gastrointestinal neoplasia. Gut 2000; 47: 251–255.
Schlemper RJ, Iwashita A. Classification of gastrointestinal epithelial neoplasia. Curr Diagn Pathol 2004; 10: 128–139.

Oesophagus

Barr H. The pathological implications of surveillance, treatment and surgery for Barrett's oesophagus. Curr Diagn Pathol 2003; 9: 242–251.

Biddlestone LR, Bailey TA, Whittles CE, Shepherd NA. The clinical and molecular pathology of Barrett's oesophagus. In: Kirkham N, Lemoine NR (eds). Progress in pathology 5. Medical Media Limited. London 2001; 57–80.
Bogomeletz WV. Early squamous cell carcinoma of oesophagus. Curr Diagn Pathol 1994; 1: 212–215.
British Society of Gastroenterology. Guidelines for the diagnosis and management of Barrett's columnar-lined oesophagus. http://www.bsg.org.uk/clinical-prac/guidelines.htm
Burroughs SH, Biffin AHB, Pye JK, Williams GT. Oesophageal and gastric cancer pathology reporting: a regional audit. J Clin Pathol 1999; 52: 435–439.
Coad RA, Shepherd NA. Barrett's oesophagus: definition, diagnosis and pathogenesis. Curr Diagn Pathol 2003; 9: 218–227.
Day DW, Dixon MF. Biopsy pathology of the oesophagus, stomach and duodenum, 2nd edn. Chapman and Hall Medical. London 1995.
Galmiche JP, Pallone F (eds). Barrett's oesophagus and oesophageal adenocarcinoma. Gut 2005; 54(Suppl. 1): i1–i42.
Ibrahim NBN. Guidelines for handling oesophageal biopsies and resection specimens and their reporting. J Clin Pathol 2000; 53: 89–94.
Lewin KJ, Appelman HD. Tumors of the esophagus and stomach. Atlas of tumor pathology. 3rd series. Fascicle 18. AFIP. Washington 1996.
Mandard AM, Dalibard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF, Roussel A et al. Pathologic assessment of tumour regression after preoperative chemoradiotherapy of oesophageal carcinoma. Cancer 1994; 73: 2680–2696.
Paraf F, Fléjou J-F, Pignon J-P, Fékété F, Potet F. Surgical pathology of adenocarcinoma arising in Barrett's esophagus. Am J Surg Pathol 1995; 19: 183–191.

Stomach

Becker K, Mueller J, Fink U, Matzen K, Sendler A, Dittler HJ, Helmberger H, Siewert JR, Höfler H. The interpretation of pathologic changes in the resection specimen following multinodal therapy for gastric adenocarcinomas. In: Progress in Gastric Cancer Research. Siewert JR, Roder JD (eds). Monduzzi: Bologna 1997; 1275–1280.
Carneiro F. Classification of gastric carcinomas. Curr Diagn Pathol 1997; 4: 51–59.
Chandrasoma P. Controversies of the cardiac mucosa and Barrett's oesophagus. Histopathology 2005; 46: 361–373.
Copie-Bergman C, Gaulard P, Lavergne-Slove A et al. Proposal for a new histological grading system for post treatment evaluation of gastric MALT lymphoma. Gut 2003; 52: 1656.
Dixon MF, Martin IG, Sue-Ling HM, Wyatt, JI, Quirke P, Johnston D. Goseki grading in gastric cancer: comparison with existing systems of grading and its reproducibility. Histopathology 1994; 25: 309–316.
Emory TS, Sobin LH, Lukes L, Lee DH, O'Leary TJ. Prognosis of gastrointestinal smooth-muscle (stromal tumors): dependence on anatomic site. Am J Surg Pathol 1999; 23: 82–87.
Feakins RM. The expression of p53 and bcl-2 in gastrointestinal stromal tumours is associated with anatomical site and p53 expression is associated with grade and clinical outcome. Histopathology 2005; 46: 270–279.
Kende AI, Carr NJ, Sobin LH. Expression of cytokeratins 7 and 20 in carcinoma of the gastrointestinal tract. Histopathology 2003; 42: 137–140.

Lauren P. The two histological main types of gastric carcinoma. Acta Pathol Microbiol Scand 1965; 64: 31–49.
Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumours of the stomach. A clinicopathologic, immunohistochemical and molecular genetic study of 1765 cases with long-term follow-up. Am J Surg Pathol 2005; 29: 52–68.
Rooney N. Gastrointestinal lymphoma. Curr Diagn Pathol. 2004; 10: 69–78.
Sabah M, Leader M, Kay E. Gastrointestinal stromal tumours: an update. Curr Diagn Pathol 2005; 11: 400–410.
Seidal T, Edvardsson H. Expression of c-kit (CD117) and Ki67 provides information about the possible cell of origin and clinical course of gastrointestinal stromal tumours. Histopathology 1999; 34: 416–424.
Siewert JR, Stein HJ. Classification of adenocarcinoma of the oesophagogastric junction. Br J Surg 1998; 25: 1457–1459.
Son HJ, Song SY, Kim S, Noh JH, Sohn TS, Kim DS, Rhee JC. Characteristics of submucosal gastric carcinoma with lymph node metastatic disease. Histopathology 2005; 46: 158–165.
Wündisch T, Neubauer A, Stolte M, Ritter M, Thiede C. B-cell monoclonality is associated with lymphoid follicles in gastritis. Am J Surg Pathol 2003; 27: 882–887.

Small intestine

Domizio P, Owen RA, Shepherd NA, Talbot IC, Norton AJ. Primary lymphoma of the small intestine. A clinicopathological study of 119 cases. Am J Surg Pathol 1993; 17: 429–442.
Fletcher CDM, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, Miettinen M, O'Leary TJ, Remotti H, Rubin BP, Shmookler B, Sobin LH, Weiss SW. Diagnosis of gastrointestinal stromal tumours a consensus approach. Hum Pathol 2002; 33: 459–465.
Isaacson PG. Gastrointestinal lymphoma. Hum Pathol 1994; 25: 1020–1029.
Lioe TF, Biggart JD. Primary adenocarcinoma of the jejunum and ileum: clinicopathological review of 25 cases. J Clin Pathol 1990; 43: 533–536.
Sircar K, Hewlett BR, Huizinga JD, Chorneyko K, Berezin I, Riddell RH. Interstitial cells of Cajal as precursors of gastrointestinal stromal tumors. Am J Surg Pathol 1999; 23: 377–389.

Colorectum

Bateman AC, Carr NJ, Warren BF. The retroperitoneal surface in distal caecal and proximal ascending colon carcinoma: the Cinderella surgical margin? J Clin Pathol 2005; 58: 426–428.
Bull AD, Biffin AHB, Mella J, Radcliffe AG, Stamatakis JD, Steele RJC, Williams GT. Colorectal cancer pathology reporting: a regional audit. J Clin Pathol 1997; 50: 138–142.
Burroughs SH, Williams GT. Examination of large intestine resection specimens. J Clin Pathol 2000; 50: 344–349.
Cooper HS, Deppisch LM, Kahn EI, Lev R, Manley PN, Pascal RR, Qizilbash AH, Rickert RR, Silverman JF, Wirman JA. Pathology of the malignant colorectal polyp. Hum Pathol 1998; 29: 15–26.
Dukes CE, Bussey HJR. The spread of rectal cancer and its effect on prognosis. Br J Cancer 1958; 12: 309–320.
Dworak O, Keilholz L, Hoffman A. Pathological features of rectal cancer after preoperative radiochemotherapy. Int J Colorect Dis 1997; 12: 19–23.
Goldstein NS. Lymph node recoveries from 2427 pT3 colorectal resection specimens spanning 454 cases. Recommendations for a minimum number

of recovered lymph nodes based on predictive probabilities. Am J Surg Pathol 2002; 26: 179–189.
Goldstein NS, Hart J. Histologic features associated with lymph node metastasis in stage T1 and superficial T2 rectal adenocarcinomas in abdominoperineal resection specimens. Am J Clin Pathol 1999; 111: 51–58.
Haggitt RC, Glotzbach RE, Soffer EE, Wruble LD. Prognostic factors in colorectal carcinomas arising in adenomas: implications for lesions removed by endoscopic polypectomy. Gastroenterology 1985; 89: 328–336.
Hurlstone DP, Brown S, Cross SS. The role of flat and depressed colorectal lesions in colorectal carcinogenesis: new insights for clinicopathological findings in high-magnification chromoscopic colonoscopy. Histopathology 2003; 43: 413–426.
Jass JR. Diagnosis of hereditary non-polyposis colorectal cancer. Histopathology 1998; 32: 491–497.
Jass JR, Young J, Leggett BA. Hyperplastic polyps and DNA microsatellite unstable cancers of the colorectum. Histopathology 2000; 37: 295–301.
Jass JR. Serrated adenoma of the colorectum. Curr Diagn Pathol 2002; 8: 42–49.
Jones DJ (eds). ABC of colorectal diseases, 2nd edn. BMJ Books. London 1999.
Kiesslich R, Neurath MF. Endoscopic mucosal resection: an evolving therapeutic strategy for non-polypoid colorectal neoplasia. Gut 2004; 53: 1222–1224.
Konishi F, Morson BC. Pathology of colorectal adenomas: a colonoscopic survey. J Clin Pathol 1982; 35: 830–841.
Ludeman L, Shepherd NA. Serosal involvement in gastrointestinal cancer: its assessment and significance. Histopathology 2005; 47: 123–131.
Morson BC, Whiteway JE, Jones EA, Macrac FA, Williams CB. Histopathology and prognosis of malignant colorectal polyps treated by endoscopic polypectomy. Gut 1984: 25; 437–444.
McGregor DK, Wu TT, Rashid A, Luthra R, Hamilton SR. Reduced expression of cytokeratin 20 in colorectal carcinomas with high levels of microsatellite instability. Am J Surg Pathol 2004; 28: 712–718.
Pheby DFH, Levine DF, Pitcher RW, Shepherd NA. Lymph node harvests directly influence the staging of colorectal cancer: evidence from a regional audit. J Clin Pathol 2004; 57: 43–47.
Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. Lancet 1986; ii: 996–998.
Quirke P. The pathologist, the surgeon and colorectal cancer: get it right because it matters. In: Kirkham N, Lemoine NR (eds). Progress in pathology 4. Churchill Livingstone. Edinburgh 1998; 201–213.
Quirke P. Training and quality assurance for rectal cancer: 20 years of data is enough. Lancet 2004; 4: 695–701.
Riddell RH, Goldman H, Ransonoff DF, Appelman HD, Fenoglio CM, Haggitt RC, Ahren C, Correa P, Hamilton SK, Morson BC, Sommers SC, Yardley JH. Dysplasia in inflammatory bowel disease: standardised classification with provisional clinical applications. Hum Pathol 1983; 14: 931–968.
Ryan R, Gibbons D, Hyland JMP, Treanor D, White A, Mulcahy HE, O'Donoghue DP, Moriarty M, Fennelly D, Sheahan K. Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. Histopathology 2005; 47: 141–146.
Shepherd NA, Baxter KJ, Love SB. Influence of local peritoneal involvement on pelvic recurrence and prognosis in rectal cancer. J Clin Pathol 1995; 48: 849–855.

Shepherd NA. Pathological prognostic factors in colorectal cancer. In: Kirkham N, Lemoine NR (eds). Progress in pathology 2. Churchill Livingstone. Edinburgh 1995; 115–141.
Shepherd NA. Polyps and polyposis syndromes of the intestines. Curr Diagn Pathol 1997; 4: 222–238.
Snover DC, Jass JR, Fenoglio-Preiser C, Batts KP. Serrated polyps of the large intestine. A morphologic and molecular review of an evolving concept. Am J Clin Pathol 2005; 124: 380–391.
Sutherland F, Haine L, Quirke P. Molecular approaches to colorectal cancer: a review. Curr Diagn Pathol 1998; 5: 34–43.
Talbot IC, Ritchie S, Leighton M, Hughes AO, Bussey HJR, Morson BC. Invasion of veins by carcinoma of rectum: method of detection, histological features and significance. Histopathology 1981; 5: 141–163.
Vasen HFA, Morreau H. Familial and hereditary colorectal cancer with emphasis on the hereditary non-polyposis colorectal cancer syndrome. Curr Diagn Pathol 2002; 8: 241–248.
Vass DG, Ainsworth R, Anderson JH, Murray D, Foulis AK. The value of an elastic tissue stain in detecting venous invasion in colorectal cancer. J Clin Pathol 2004; 57: 769–772.
Wheeler JM, Warren BF, Mortensen NJ. Quantification of histologic regression of rectal cancer after irradiation: a proposal for a modified staging system. Dis Colon Rectum 2002; 45: 1051–1056.
Wong NACS, Mayer NJ, Mackell S, Gilmour HM, Harrison DJ. Immunohistological assessment of Ki-67 and p53 expression assists the diagnosis and grading of ulcerative colitis-related dysplasia. Histopathology 2000; 37: 108–114.

Appendix

Anderson NH, Somerville JE, Johnston CF, Hayes DM, Buchanan KD, Sloan JM. Appendiceal goblet cell carcinoids: a clinicopathological and immunohistochemical study. Histopathology 1991; 18: 61–65.
Burke AP, Sobin LH, Federspiel BH, Shekitka KM, Helwig FB. Goblet cell carcinoids and related tumours of the vermiform appendix. Am J Clin Pathol 1990; 94: 27–35.
Carr NJ, McCarthy WF, Sobin LH. Epithelial and noncarcinoid tumors and tumor-like lesions of the appendix. Cancer 1995; 75: 757–768.
Misdraji J, Yantiss RK, Graeme-Cook FM, Baliss UJ, Young RH. Appendiceal mucinous neoplasm: a clinicopathologic analysis of 107 cases. Am J Surg Pathol 2003; 27: 1089–1103.
Misdraji J. Epithelial neoplasms and other epithelial lesions of the appendix (excluding carcinoid tumours). Curr Diagn Pathol 2005; 11: 60–71.
Misdraji J. Neuroendocrine tumours of the appendix. Curr Diagn Pathol 2005; 11: 180–193.
Ronnett BM, Kurman RJ, Shmookler BM, Sugarbaker PH, Young RH. The morphologic spectrum of ovarian metastases of appendiceal adenocarcinomas. Am J Surg Pathol 1997; 21: 1144–1155.

Anus and pelvic exenteration

Goldblum JR, Hart WR. Perianal Paget's disease. A histologic and immunohistochemical study of 11 cases with and without associated rectal adenocarcinoma. Am J Surg Pathol 1998; 22: 170–179.
Rodrigues-Bigas Ma, Petrelli NJ. Pelvic exenteration and its modifications. Am J Surg 1996; 171: 293–298.

Temple WJ, Saettler EB. Locally recurrent rectal cancer: role of composite resection of extensive pelvic tumours with strategies for minimizing risk of recurrence. J Surg Oncol 2000; 73: 47–58.
Williams GR, Sheffield JP, Love SB, Talbot IC. Morphology of anal carcinoma: a reappraisal. Curr Diagn Pathol 1995; 2: 32–37.
Williams GR, Talbot IC. Anal carcinoma: a histological review. Histopathology 1994; 25: 507–516.

Pancreas, gall bladder, liver and extrahepatic bile ducts

Albores-Saavedra J, Henson DE, Klimstra DS. Tumors of the gall bladder, extrahepatic bile ducts and ampulla of Vater. Atlas of tumor pathology, 3rd series. Fascicle 27. AFIP. Washington 2000.
Alsaad K, Chetty R. Serous cystic neoplasms of the pancreas. Curr Diagn Pathol 2005; 11: 102–109.
Andea AA, Basturk O, Adsay NV. Pancreatic intra-epithelial neoplasia: current clinicopathological and molecular considerations. Curr Diagn Pathol 2005; 11: 80–94.
Anthony PP. Hepatocellular carcinoma: an overview. Histopathology 2001; 39: 109–118.
Anthony PP. A guide to tumours in the liver. CPD Bulletin Cellular Pathology 2001; 3: 83–88.
Bateman AC. How to handle and report pancreatic specimens. CPD Bulletin Cellular Pathology 2001; 3: 94–98.
Beckingham IJ (ed). ABC of liver, pancreas and gall bladder diseases. BMJ Books. London 2001.
British Society of Gastroenterology. Guidelines for the management of patients with pancreatic cancer, periampullary and ampullary carcinomas. Gut 2005; 54: v1–v15.
Evans DB, Rich TA, Byrd DR et al. Preoperative chemoradiation and pancreatectomy for adenocarcinoma of the pancreas. Arch Surg 1992; 127: 1335–1339.
Foulis AK. Problems in the diagnosis of pancreatic neoplasia. CPD Bulletin Cellular Pathology 2001; 3: 99–102.
Foulis K. Pathology of the endocrine pancreas. CPD Bulletin Cellular Pathology 2002; 4: 153–156.
Govender G. Mucinous cystic neoplasms of the pancreas. Curr Diagn Pathol 2005; 11: 110–116.
Hruban RH, Takaori K, Klimstra DS, Adsay NV et al. An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. Am J Surg Pathol 2004; 28: 977–987.
Ishak KG, Goodman ZD, Stocker JT. Tumors of the liver and intrahepatic bile ducts. Atlas of tumor pathology. 3rd series. Fascicle 31. AFIP. Washington 2001.
Kakar S, Burgart LJ. Tumours of the biliary system. Curr Diagn Pathol 2005; 11: 34–43.
Lau SK, Weiss LM, Chu PG. Differential expression of MUC1, MUC2 and MUC5 AC in carcinomas of various sites. An immunohistochemical study. Am J Clin Pathol 2004; 122: 61–69.
Levi E, Klimstra DS, Adsay NV, Andea A, Basturk O. MUC1 and MUC2 in pancreatic neoplasia. J Clin Pathol 2004; 57: 456–462.
MacSween RNM, Burt AD, Portmann BC, Ishak KG, Scheuer PJ, Anthony PP (eds). Pathology of the liver, 4th edn. Churchill Livingstone. London 2002.

Paterson AC, Cooper K. Tumours and tumour-like lesions of the hepatic parenchyma. Curr Diagn Pathol 2005; 11: 19–53.
Quaglia A, Battacharjya S, Dhillon P. Limitations of the histopathological diagnosis and prognostic assessment of hepatocellular carcinoma. Histopathology 2001; 38: 167–174.
Ramage JK, Davies AHG, Ardill F et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours. Gut 2005; 54: iv1–iv16.
Ryder S. Predicting survival in early hepatocellular carcinoma. Gut 2005; 54: 328–329.
Standish RA, Davies SE. Bile duct tumours. Curr Diagn Pathol 2002; 8: 160–171.
Solcia E, Capella C, Klöppel G. Tumors of the pancreas. Atlas of tumor pathology, 3rd series. Fascicle 20. AFIP. Washington 1997.
Takhar AS, Palaniappan P, Dhingse R, Lobo DN. Recent development in diagnosis of pancreatic cancer. 2004; 329: 668–673.
Warren BF. Pathology of the gall bladder. CPD Bulletin Cellular Pathology 2001; 3: 103–105.

HEAD AND NECK CANCER

Asa SL. My approach to oncocytic tumours of the thyroid. J Clin Pathol 2004; 57: 225–232.
Anderson CE, McLaren KM. Best practice in thyroid pathology. J Clin Pathol 2004; 56: 401–405.
Baloch ZW, Livolsi VA. Newly described tumours of the thyroid. Curr Diagn Pathol 2000; 6: 151–164.
Barnest L, Eveson J, Reichart P, Sidransky D (eds). World Health Organisation Classification of Tumours. Pathology and Genetics. Tumours of the Head and Neck. IARC Press. Lyon 2005.
Barrett AW, Speight PM. Diagnostic problems in oral mucosal pathology and how to approach them. CPD Bulletin Cellular Pathology 2001; 3: 17–21.
British Association of Otorhinolarngologists—Head and Neck Surgeons. Effective head and neck cancer management. Second Consensus Document. Royal College of Surgeons. London 2000.
Buley ID. Malignancy in the thyroid gland. CPD Bulletin Cellular Pathology 2002; 4: 145–149.
DeLellis RA. Tumors of the parathyroid gland. Atlas of tumor pathology. 3rd series. Fascicle 6. AFIP. Washington 1993.
Derringer GA, Thompson LDR, Frommett RA, Bijwaard KE, Hefess CS, Abbondanzo SL. Malignant lymphoma of the thyroid gland. A clinicopathologic study of 108 cases. Am J Surg Pathol 2000; 24: 623–639.
Ellis G, Auclair P. Tumors of the salivary glands. Atlas of tumor pathology. 3rd series. Fascicle 17. AFIP. Washington 1996.
Eveson JW. Difficult differential diagnoses in salivary gland tumours. CPD Bulletin Cellular Pathology 2001; 3: 9–12.
Friedmann I (ed). Nose, throat and ears. Systemic pathology, 3rd edn. Vol 1. Churchill Livingstone. Edinburgh 1986.
Gnepp DR (ed). Diagnostic surgical pathology of the head and neck. WB Saunders. Philadelphia 2001.
Helliwell TR. ACP Best Practice No. 157. Guidelines for the laboratory handling of laryngectomy specimens. J Clin Pathol 2000; 53: 171–176.
Johnson SJ, Sheffield EA, McNichol AM. Examination of parathyroid gland specimens. ACP Best Practice No 183. J Clin Pathol 2005; 58: 338–342.

Kocjan G. Pitfalls in fine needle aspiration cytology (FNAC) of endocrine organs. Part 1—the thyroid gland. CPD Bulletin Cellular Pathology 2002; 4: 127–129.
MacDonald DG, Browne RM. Tumours of odontogenic epithelium. In: Anthony PP, MacSween RNM (eds). Recent advances in histopathology 17. Churchill Livingstone. Edinburgh 1997; 139–166.
McNichol AM. Criteria for diagnosis of follicular thyroid neoplasms and related conditions. In: Lowe DG, Underwood JCE (eds). Recent advances in histopathology. Volume 20. RSM Press. London 2003; 1–16.
Milford C. Practical anatomy of the nose and paranasal sinuses for surgical pathologists. CPD Bulletin Cellular Pathology 2001; 3: 6–8.
Millard PR. How to report a laryngeal carcinoma. CPD Bulletin Cellular Pathology 2001; 3: 41–44.
Nishida T, Katayama S, Tsujimoto M, Nakamura J, Matsuda H. Clinicopathological significance of poorly differentiated thyroid carcinoma. Am J Surg Pathol 1999; 23: 205–211.
Perez-Odonez B. Selected topics in salivary gland tumour pathology. Curr Diagn Pathol 2004; 9: 355–365.
Rosai J, Carcangiu ML, DeLellis RA. Tumors of the thyroid gland. Atlas of tumor pathology. 3rd series. Fascicle 5. AFIP. Washington 1992.
Shah KA. Cytology of head and neck lesions. Classical features and pitfalls. CPD Bulletin Cellular Pathology 2001; 3: 17–21.
Simpson RHW. Salivary gland tumours. In: Anthony PP, MacSween RNM (eds). Recent advances in histopathology 17. Churchill Livingstone. Edinburgh 1997; 167–190.
Simpson RHW, Sarsfield PTL. Benign and malignant lymphoid lesions of the salivary glands. Curr Diagn Pathol 1997; 4: 91–99.
Slootweg PJ. Complex head and neck specimens and neck dissections. How to handle them. ACP Best Practice No 182. J Clin Pathol 2005; 58: 243–248.
Sobrinho-Simóes M, Magalháes J, Fonseca E, Amendoeira I. Diagnostic pitfalls of thyroid pathology. Curr Diagn Pathol 2005; 11: 52–61.
Speight PM, Farthing PM, Bouquot JE. The pathology of oral cancer and precancer. Curr Diagn Pathol 1996; 3: 165–176.
Stephenson TJ. Benign lesions and mimics of malignancy in the thyroid gland. CPD Bulletin Cellular Pathology 2002; 4: 139–144.
Thompson LDR. Squamous cell carcinoma variants of the head and neck. Curr Diagn Pathol 2003; 9: 384–396.
Young JA. Diagnostic problems in fine needle aspiration cytopathology of the salivary glands. J Clin Pathol 1994; 47: 193–198.

RESPIRATORY AND MEDIASTINAL CANCER

Abutaily AS, Addis BJ, Roche WR. Immunohistochemistry in the distinction between malignant mesothelioma and pulmonary adenocarcinoma: a central evaluation of new antibodies. J Clin Pathol 2002; 55: 662–668.
Attanoos RL. Management of small biopsies in pulmonary diseases. CPD Bulletin Cellular Pathology. 2000; 2: 138–141.
Attanoos RL. Pitfalls in pulmonary pathology. Curr Diagn Pathol 2005; 11: 44–51.
Attanoos RL, Gibbs AR. Asbestos-related deaths. Curr Diagn Pathol 2002; 8: 373–383.
Attanoos RL, Gibbs AR. Asbestos-related neoplasia. In: Lowe DG, Underwood JCE (eds). Recent advances in histopathology. Volume 20. RSM Press. London 2003; 73–78.

Attanoos RL, Gibbs AR. The pathology associated with therapeutic procedures in malignant mesothelioma. Histopathology 2004; 45: 393–397.

Battifora H, McCaughey WT. Tumors of the serosal membranes. Atlas of tumor pathology. 3rd series. Fascicle 15. AFIP. Washington 1995.

Burnett RA, Swanson Beck J, Howatson SR, Lee FD, Lessells AM, McLaren KM, Ogston S, Robertson AJ, Simpson JG, Smith GD, Tavadia HB, Walker F. Observer variability in histopathological reporting of malignant bronchial biopsy specimens. J Clin Pathol 1994; 47: 711–713.

Carey FA. Pulmonary adenocarcinoma. Curr Diagn Pathol 2001; 7: 187–193.

Clelland CA. Malignant lung tumours. CPD Bulletin Cellular Pathology 2000; 2: 148–153.

Colby TV, Koss MN. Tumors of the lower respiratory tract. Atlas of tumor pathology. 3rd series. Fascicle 13. AFIP. Washington 1995.

Corrin B. Pathology of the lungs, 1st edn. Churchill Livingstone. London: 2000.

Corrin B, Nicholson AG. Pathology of the lungs, 2nd edn. Churchill Livingstone Elsevier. London 2006.

Corrin B. Neuroendocrine neoplasms of the lung. Curr Diagn Pathol 1997; 4: 239–250.

Corrin B (ed). Pathology of Lung Tumours. Churchill Livingstone. New York 1997.

Flieder DB. Recent advances in the diagnosis of adenocarcinoma: the impact of lung cancer screening on histopathologists. Curr Diagn Pathol 2004; 10: 269–278.

Gosney JR. Endocrine pathology of the lung. In: Anthony PP, MacSween RNM (eds). Recent advances in histopathology 16. Churchill Livingstone. Edinburgh 1994; 147–165.

Gray W. Pulmonary cytology—classical features and pitfalls. CPD Bulletin Cellular Pathology 2002; 2: 154–160.

Hasleton PS, Hammar SP. Malignant mesothelioma. Curr Diagn Pathol 1996; 3: 153–164.

Herbert A. Cytology of metastatic neoplasia in the lung. In: Lowe DG, Underwood JCE (eds). Recent advances in histopathology 18. Churchill Livingstone. Edinburgh 1999; 109–116.

Kerr KM. Morphology and genetics of pre-invasive pulmonary disease. Curr Diagn Pathol 2004; 10: 259–268.

Kitamura H, Kameda Y, Ito T, Hayashi H. Atypical adenomatous hyperplasia of the lung. Implications for the pathogenesis of peripheral lung adenocarcinoma. Am J Clin Pathol 1999; 111: 610–622.

Marino M, Müller-Hermelink HK. Thymoma and thymic carcinoma: relation of thymic epithelial cells to the cortical and medullary differentiation of thymus. Virchows Arch 1985; 407: 119–126.

Marson JV, Mazieres J, Groussard O, Garcia O, Berjaud J, Dahan M, Carles P, Daste G. Expression of TTF-1 and cytokeratins in primary and secondary epithelial lung tumours: correlation with histological type and grade. Histopathology 2004; 45: 125–134.

Masaoka A, Monden Y, Nakahara K, Tanioka T. Follow-up study of thymomas with special reference to their clinical stages. Cancer 1981; 48: 2485–2492.

Mayer NJ, Wallace WAH, Kamel HM. Nodular lesions of the lung: a practical approach to histological diagnosis. Curr Diagn Pathol 2003; 9: 188–198.

Müller-Hermelink HK, Marx A, Kirchner Th. Advances in the diagnosis and classification of thymic epithelial tumours. In: Anthony PP, MacSween RNM (eds). Recent advances in histopathology 16. Churchill Livingstone. Edinburgh 1994; 49–72.

Nash G, Otis CN. Protocol for the examination of specimens from patients with malignant pleural mesothelioma. Arch Pathol Lab Med 1999; 123: 39–44.
Nicholson AG. The role of immunohistochemistry in differentiating tumours presenting in the pleura. CPD Bulletin Cellular Pathology 1999; 1(4): 149–153.
Nicholson AG. Pulmonary lymphoproliferative disorders. Curr Diagn Pathol 2000; 6: 130–139.
Olszewski W. Aspiration biopsy of intrathoracic lesions. Curr Diagn Pathol 1995; 2: 146–152.
Ordonez NG. The immunohistochemical diagnosis of mesothelioma. A comparative study of epithelioid mesothelioma and lung adenocarcinoma. Am J Surg Pathol 2003; 27: 1031–1051.
Travis WD, Brambilla E, Müller-Heimelink HK, Harris CC (eds). World Health Organisation Classification of Tumours. Pathology and Genetics. Tumours of the lung, pleura, thymus and heart. IARC Press. Lyon 2004.
Yamakawa Y, Masuoka A, Hashimoto T, Niwa H, Mizuno T, Fujii Y, Nakahara K. A tentative tumour-node-metastasis classification of thymoma. Cancer 1991; 68: 1984–1987.

SKIN CANCER

Balch CM, Buzaid AC, Soong SJ, Atkins MB, Cascinelli N, Colt DG, Fleming ID, Gershenwald JE, Houghton A Jr, Kirkwood JK, McMasters KM, Mihn MF, Morton DL, Reintgen DS, Ross MI, Sober A, Thompson JA, Thompson JF. Final version of the American Joint Committee on cancer staging system for cutaneous melanoma. J Clin Oncol 2001; 19 (16): 3635–3648.
Banerjee SS, Harris M. Morphological and immunophenotypic variations in malignant melanoma. Histopathology 2000; 36: 387–402.
Blessing K. Benign atypical naevi: diagnostic difficulties and continued controversy. Histopathology 1999; 34: 189–198.
Breslow A. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. Ann Surg 1970; 172: 902–908.
Cerroni L, Kerl H, Gatter K. An illustrated guide to skin lymphoma. Blackwell Scientific. Oxford 1998.
Clark WH Jr. A classification of malignant melanoma in man correlated with histogenesis and biological behaviour. In: Montagna W, Hu F (eds).Advances in Biology of the Skin. Vol. 8. Pergamon Press. London 1967; 621–627.
Cochran AJ, Bailly C, Cook M, Crotty K, Mihm M, Mooi W, Sagebiel R. Recommendations for the reporting of tissues removed as part of the surgical treatment of cutaneous melanoma. Hum Pathol 1997; 28: 1123–1125.
Cook MG. Problems in the histological assessment of melanoma emphasising the importance of the vertical/nodular component. Curr Diagn Pathol 1994; 1: 98–104.
Cook MG. A practical approach to spindle cell melanocytic lesions. CPD Bulletin Cellular Pathology 1999; 1(3): 101–104.
Cook MG, Clarke TJ, Humphreys S, Fletcher A, McLaren KM, Smith NP, Stevens A, Theaker JM, Melia J. The evaluation of diagnostic and prognostic criteria and the terminology of thin cutaneous malignant melanoma by the CRC Melanoma Pathology Panel. Histopathology 1996; 28: 497–512.
Cook MG. Sentinel lymph node biopsy for melanoma. Curr Diagn Pathol 2003; 9: 296–301.
Cook MG. Diagnostic pitfalls with melanocytic tumours. Curr Diagn Pathol 2004; 10: 463–472.
Culpepper KS, Granter SR, McKee PH. My approach to atypical melanocytic lesions. J Clin Pathol 2004; 57: 1121–1131.

DeWit NJW, Van Muijen GNP, Ruiter DJ. Immunohistochemistry in melanocytic proliferative lesions. Histopathology 2004; 44: 517–541.
Edwards SL, Blessing K. Problematic pigmented lesions: approach to diagnosis. J Clin Pathol 2000; 53: 409–418.
Elder DE, Murphy GF. Melanocytic tumors of the skin. Atlas of tumor pathology. 3rd series. Fascicle 2. AFIP. Washington 1991.
Elder DE, Johnson B, Elenitsas R. Lever's Histopathology of the Skin, 9th edn. Lippincott, Williams and Wilkins. Philadelphia 2004.
Goodland JR, Hollowood K. Primary cutaneous B-cell lymphoma. Curr Diagn Pathol 2001; 7: 33–40.
Hollowood K. The diagnosis of sweat gland carcinomas: a practical approach. CPD Bulletin Cellular Pathology 1999; 1(3): 105–110.
Kirkham N. Malignant melanoma: progress in diagnosis and prognosis. In: Kirkham N, Lemoine NR (eds). Progress in pathology 4. Churchill Livingstone. Edinburgh 1998; 241–253.
Kirkham N. Optimal handling and criteria for melanoma diagnosis. Histopathology 2000; 37: 464–472.
Kirkham N. The differential diagnosis of thin malignant melanoma. Curr Diagn Pathol 2003; 9: 281–286.
McKee PH, Calonje E, Granter SR. Pathology of the skin with clinical correlations, 3rd edn. Mosby. London 2005.
Mooi WJ. The dysplastic naevus. J Clin Pathol 1997; 50: 711–715.
Motley R, Kersey P, Lawrence C. Multiprofessional guidelines for the management of the patient with primary cutaneous squamous cell carcinoma. Br J Dermatol 2002; 146(1): 18–25.
Murphy GF, Elder DE. Non-melanocytic tumors of the skin. Atlas of tumor pathology. 3rd series. Fascicle 1. AFIP. Washington 1991.
Rippey JJ. Why classify basal cell carcinomas? Histopathology 1998; 32: 393–398.
Sakkinen P, Kohler S. Histologic mimickers of thick melanoma. Curr Diagn Pathol 2003; 9: 287–295.
Sanders DSA, Blessing K. Guidelines on reporting cutaneous malignant melanoma. CPD Bulletin Cellular Pathology 1999; 1(3): 97–100.
Slater DN. Classification and diagnosis of cutaneous lymphoproliferative disorders. In: Lowe DG, Underwood SCE (eds). Recent Advances in Histopathology 20. RSM Press. London 2003; 53–72.
Spatz A, Shaw HM, Crotty KA, Thompson JF, McCarthy SW. Analysis of histopathological factors associated with prolonged survival of 10 years or more for patients with thick melanomas (>5 mm). Histopathology 1998; 33: 406–413.
Weedon D, LeBoit P, Burg G, Sarasin A (eds). World Health Organisation Classification of Tumours. Pathology and Genetics. Tumours of the Skin. IARC Press. Lyon 2005.
Weedon D. Skin Pathology, 2nd edn. Churchill Livingstone. London 2002.
Willemze R, Meijer CJLM. Classification of cutaneous lymphomas: crosstalk between pathologist and clinician. Curr Diagn Pathol 1998; 5: 23–33.

BREAST CANCER

Al-Nafussi A. Spindle cell tumours of the breast: practical approach to diagnosis. Histopathology 1999; 35: 1–13.
Anderson TJ, Page DL. Risk assessment in breast cancer. In: Anthony PP, MacSween RNM (eds). Recent advances in histopathology 17. Churchill Livingstone. Edinburgh 1997; 69–91.

Bloom HJG, Richardson WW. Histological grading and prognosis in breast carcinoma: a study of 1049 cases of which 359 have been followed for 15 years. Br J Cancer 1957; 11: 359–377.
Boecker W, Buerger H. Usual and atypical ductal hyperplasia—members of the same family? Curr Diagn Pathol 2004; 10: 175–182.
Cserni G. A model for determining the optimum histology of the sentinel lymph nodes in breast cancer. J Clin Pathol 2004; 57: 467–471.
Dahlstrom JE, Sutton S, Jain S. Histological precision of stereotactic core biopsy in diagnosis of malignant and premalignant breast lesions. Histopathology 1996; 29: 537–541.
Dixon M. ABC of breast diseases, 2nd edn. BMJ Books. London 2000.
Douglas-Jones AG, Gupta SK, Attanoos RL, Morgan JM, Mansel RE. A critical appraisal of six modern classifications of ductal carcinoma in situ of the breast (DCIS): correlation with grade of associated invasive carcinoma. Histopathology 1996; 29: 397–409.
Ellis IO, Bartlett J, Dowsett M, Humphreys S, Jasani B, Miller K, Pinder SE, Rhodes A, Walker R. Updated recommendations for HER2 testing in the UK. Best Practice No 176. J Clin Pathol 2004; 57: 233–237.
Ellis IO, Humphreys S, Michell M, Pinder SE, Wells CA, Zakhour HD. Guidelines for breast needle core biopsy handling and reporting in breast screening assessment. Best Practice No 179. J Clin Pathol 2004; 57: 897–902.
Elston CW, Ellis IO. Pathological prognostic factors in breast cancer: experience from a long study with long-term follow-up. Histopathology 1991; 19: 403–410.
Elston CW, Ellis IO (eds). The Breast. Systemic Pathology, 3rd edn. Vol. 13. Churchill Livingstone. Edinburgh 1998.
Fitzgibbins PL, Page DL, Weaver D et al. Prognostic factors in breast cancer. College of American Pathologists consensus statement 1999. Arch Pathol Lab Med 2000; 124: 966–978.
Fulford LG, Reis-Filho JS, Lakhani SR. Lobular in-situ neoplasia. Curr Diagn Pathol 2004; 10: 183–192.
Harris G, Pinders S, Ellis I. Ductal carcinoma in-situ: diagnosis and classification. Curr Diagn Pathol 2004; 10: 204–210.
Kennedy M, Masterson AV, Kerin M, Flanagan F. Pathology and clinical relevance of radial scars: a review. J Clin Pathol 2003; 56: 721–724.
Koker MM, Kleer CG. P63 expression in breast cancer. A highly sensitive and specific marker of metaplastic carcinoma. Am J Surg Pathol 2004; 28: 1506–1512.
Lagios MD, Westdahl PR, Margolin FR, Roses MR. Duct carcinoma in-situ; relationship of extent of non-invasive disease to the frequency of occult invasion, multicentricity, lymph node metastases, and short-term treatment failures. Cancer 1982; 50: 1309–1314.
Lee AHS, Denley HE, Pinder, SE, Ellis IO, Elston CW, Vujovic P, Macmillan RD, Evans AJ for the Nottingham Breast Team. Excision biopsy findings of patients with breast needle core biopsies reported as suspicious of malignancy (B4) or lesion of uncertain malignant potential (B3). Histopathology 2003; 42: 331–336.
Lerwill MF. Current practical applications of diagnostic immunohistochemistry in breast pathology. Am J Surg Pathol 2004; 28: 1076–1091.
Lewis F, Jackson P, Lane S, Coast G, Hanby AM. Testing for HER 2 in breast cancer. Histopathology 2004; 45: 207–217.
Lloyd J, Flanagan AM. Mammary and extramammary Paget's disease. J Clin Pathol 2000; 53: 742–749.
Moffat CJC, Pinder SE, Dixon AR, Elston CW, Blamey RW, Ellis IO. Phyllodes

tumours of the breast: a clinicopathological review of thirty-two cases. Histopathology 1995; 27: 205–218.
Nadji M, Gomez-Fernandez C, Ganjei-Azar P, Morales AR. Immunohistochemistry of estrogen and progesterone receptors reconsidered. Experience with 5993 cases. Am J Clin Pathol 2005; 123: 21–27.
NHSBSP publication no 50. June 2001. Guidelines for non-operative diagnostic procedures and reporting in breast cancer screening.
NHSBSP publication no 58. January 2005. Pathology reporting of breast disease. NHS Cancer Screening Programmes and The Royal College of Pathologists 2005.
Page DL, Anderson TJ. Diagnostic Histopathology of the Breast. Churchill Livingstone. Edinburgh 1987.
Pinder DL, Ellis IO, Galea M, O'Rourke S, Blamey RW, Elston CW. Pathological prognostic factors in the breast cancer. III Vascular invasion: relationship with recurrence and survival in a large study with long term follow-up. Histopathology 1994; 24: 41–47.
Pinder SE, Ellis IO, Elston CW. Prognostic factors in primary breast carcinoma. J Clin Pathol 1995; 48: 981–983.
Pinder SE, Elston CW, Ellis IO. The role of the pre-operative diagnosis in breast cancer. Histopathology 1996; 28: 563–566.
Quinn CM. The pathology of breast screening. Curr Diagn Pathol 2001; 7: 81–90.
Rosen's Breast Pathology, 2nd edn. Lippincott Williams and Wilkins. Philadelphia 2001.
Rosen PP. Breast Pathology: Diagnosis by Needle Core Biopsy. Lippincott Williams and Wilkins. Philadelphia 1999.
Rosen PP, Oberman HA. Tumors of the mammary gland. Atlas of tumor pathology. 3rd series. Fascicle 7. AFIP. Washington 1993.
Sainsbury JRC, Anderson TJ, Morgan DAL. ABC of breast diseases. Breast cancer. BMJ 2000; 321: 745–750.
Schnitt SJ. Columnar cell lesions of the breast: pathological features and clinical significance. Curr Diagn Pathol 2004; 10: 193–203.
Shousha S. Diagnosis of "early", "minimal" and impalpable breast carcinoma. Curr Diagn Pathol, 1994; 1: 90–97.
Shousha A. Reporting breast biopsies. Curr Diagn Pathol 2000; 6: 140–145.
Sloane JP, Lakhani SR. Atypical hyperplasias and DCIS: recognition and classification. CPD Bulletin Cellular Pathology 2000; 2: 72–75.
Smitt MC, Nowels KW, Zdeblick MJ et al. The importance of the lumpectomy surgical margin status in long-term results of breast conservation. Cancer 1995; 76: 259–267.
Tavassoli FA, Devilee P (eds). World Health Organization Classification of Tumours, Pathology and Genetics. Tumours of the Breast and Female Genital Organs. IARC Press. Lyon 2003.
Turner RR, Ollila DW, Stern S, Giulano A. Optimal histopathologic examination of the sentinel lymph node for breast carcinoma staging. Am J Surg Pathol 1999; 23: 263–267.
UK National Coordinating Group for Breast Screening Pathology. Consistency of histopathological reporting of breast lesions detected by screening: findings of the UK National external quality assessment (EQA) scheme. Eur J Cancer 1994; 30: 1414–1419.
Van Diest PJ. Histopathological workup of sentinel lymph nodes: how much is enough? J Clin Pathol 1999; 52: 871–873.
Westenend PJ, Meurs CJC, Damhuis RAM. Tumour size and vascular invasion predict distant metastases in stage I breast cancer. Grade distinguishes early and late metastases. J Clin Pathol 2005; 58: 196–201.

GYNAECOLOGICAL CANCER

Cheung ANY, Ip PPC. Iatrogenic lesions of the female genital tract. Curr Diagn Pathol 2003; 9: 105–113.

Clement PB, Young RH. Atlas of Gynecologic Pathology. Saunders. Philadelphia 2000.

Fox H, Wells M (eds). Haines and Taylor's obstetrical and gynaecological pathology, 5th edn. Churchill Livingstone Elsevier. New York 2003.

Lowe DG, Buckley CH, Fox H. Advances in gynaecological pathology. In: Anthony PP, MacSween RNM (eds). Recent advances in histopathology 17. Churchill Livingstone. Edinburgh 1997; 113–137.

Manek S. Immunohistochemistry in gynaecological diseases. CPD Bulletin Cellular Pathology 1999; 1(4): 162–166.

McCluggage WG. Recent advances in immunohistochemistry in gynaecological pathology. Histopathology 2002; 40: 309–326.

McCluggage WG. Metaplasia in the female genital tract. In: Lowe DG, Underwood JCE (eds). Recent Advances in Histpathology 20. RSM Press. London 2003; 29–52.

Robboy SJ, Anderson MC, Russell PR. Pathology of the female reproductive tract. Churchill Livingstone. London 2002.

Tavassoli FA, Devilee P (eds). World Health Organisation Classification of Tumours. Pathology and Genetics. Tumours of the Breast and Female Genital organs. IARC Press. Lyon 2003; 113–364.

Young RH, Clement PB (eds). Recent advances in gynaecological pathology. Hum Pathol 1991; 22: 737–806, 847–891.

Ovary

Al-Nafussi A. Ovarian epithelial tumours: common problems in diagnosis. Curr Diagn Pathol 2004; 10: 473–499.

Bell KA, Smith Sehdev AE, Kurman RJ. Refined diagnostic criteria for implants associated with ovarian atypical proliferative serous tumours (borderline) and micropapillary serous carcinomas. Am J Surg Pathol 2001; 25: 419–432.

Eichorn JH, Bell DA, Young RH, Scully RE. Ovarian serous borderline tumours with micropapillary and cribriform patterns. A study of 40 cases and comparison with 44 cases without these patterns. Am J Surg Pathol 1999; 23: 397–409.

Expert opinion. Serous borderline tumours of the ovary. Histopathology 2005; 47: 310–318.

Feeley KM, Wells M. Precursor lesions of ovarian epithelial malignancy. Histopathology 2001; 38: 87–95.

Fox H. Primary neoplasia of the female peritoneum. Histopathology 1993; 23: 103–110.

Fox H. Ovarian tumours of borderline malignancy: time for a reappraisal? Curr Diagn Pathol 1996; 3: 143–151.

Fox H. Ploidy in gynaecological cancers. Histopathology 2005; 46: 121–129.

Kasprzak L, Foulkes WD, Shelling AN. Hereditary ovarian carcinoma. BMJ 1999; 318: 786–789.

Kempson RL, Foulkes WD, Shelling AN. Ovarian serous borderline tumors: the citadel defended. Hum Pathol 2000; 31: 525–526.

Lagendijk JH, Mullink H, van Diest PJ, Meijer GA, Meijer CJLM. Immunohistochemical differentiation between primary adenocarcinoma of the ovary and ovarian metastases of colonic and breast origin. Comparison between a statistical and an intuitive approach. J Clin Pathol 1999; 52: 283–290.

Lee KR, Young RH. The distinction between primary and metastatic mucinous carcinomas of the ovary. Gross and histologic findings in 50 cases. Am J Surg Pathol 2003; 27: 281–292.
Manek S, Wells M. Borderline ovarian tumours. CPD Bulletin Cellular Pathology 1998; 1(1): 11–14.
McCluggage WG, Wilkinson N. Metastatic neoplasms involving the ovary: a review with an emphasis on morphological and immunohistochemical features. Histopathology 2005; 47: 231–247.
Mount SL, Eltabbakh GH, Cooper K. Recent "non-gynaecological" immunohistochemical markers in diagnostic ovarian pathology. Curr Diagn Pathol 2003; 9: 11–18.
Riopel MA, Ronnett BM, Kurman RJ. Evaluation of diagnostic criteria and behaviour of ovarian intestinal-type mucinous tumors. Atypical proliferative (borderline) tumors and intraepithelial, microinvasive, invasive and metastatic carcinomas. Am J Surg Pathol 1999; 23: 617–635.
Rodriguez JM, Prat J. Mucinous tumours of the ovary. A clinicopathologic analysis of 75 borderline tumous (of intestinal type) and carcinomas. Am J Surg Pathol 2002; 26: 139–152.
Russell P, Farnsworth A. Surgical pathology of the ovaries, 2nd edn. Churchill Livingstone. New York 1997.
Scully RE, Young RH, Clement PB. Tumors of the ovary, maldeveloped gonads, fallopian tube and broad ligament. In: Atlas of tumour pathology. 3rd series. Fascicle 23. AFIP. Washington 1998.
Seidman JD, Ronnett BM, Kurman RJ. Evolution of the concept and terminology of borderline ovarian tumours. Curr Diagn Pathol 2000; 6: 31–37.
Silverberg SG. Histopathologic grading of ovarian carcinoma: a review and proposal. Int J Gynaecol Pathol 2000; 12: 27–15.
Silverberg SG, Bell DA, Kurman RJ, Seidman JD, Prat J, Ronnett BM, Copeland L, Silva E, Gorstein F, Young RH. Borderline ovarian tumors: key points and workshop summary. Hum Pathol 2004; 35: 910–917.
Young RH, Gilks CB, Scully RE. Mucinous tumors of the appendix associated with mucinous tumors of the ovary and pseudomyxoma peritonei: a clinicopathologic analysis of 22 cases supporting an origin in the appendix. Am J Surg Pathol 1991; 15: 415–429.
Young RH. New and unusual aspects of ovarian germ cell tumours. Am J Surg Pathol 1993; 17: 1210–1224.

Uterus

Al-Nafussi A. Uterine smooth muscle tumours: practical approach to diagnosis. Curr Diagn Pathol 2004; 10: 140–156.
Ambros RA, Sherman ME, Zahn CM, Bitterman P, Kurman RJ. Endometrial intraepithelial carcinoma: a distinctive lesion specifically associated with tumors displaying serous differentiation. Hum Pathol 1995; 26: 1260–1267.
Baak JPA, Mutter GL. EIN and WHO 94. J Clin Pathol 2005; 58: 1–6.
Bell SW, Kempson RL, Hendrickson MR. Problematic uterine smooth muscle neoplasms. Am J Surg Pathol 1994; 18: 535–558.
Buckley CH, Fox H. Biopsy pathology of the endometrium. Chapman and Hall Medical. London 1989.
Burton JL, Wells M. Recent advances in the histopathology and molecular pathology of carcinoma of the endometrium. Histopathology 1998; 33: 297–303.
Darvishian F, Hummer AJ, Thaler HT, Bhargava R, Linkov I, Soslow RA. Serous endometrial cancers that mimic endometrial adenocarcinoma. Am J Surg Pathol 2004; 28: 1568–1578.

Feeley KM, Burton JL, Wells M. A diagnostic approach to endometrial biopsies: selected topics. Curr Diagn Pathol 2000; 6: 13–20.
Fox H. Endometrial hyperplasia. Curr Diag Pathol 1994; 1: 151–157.
Fox H. Trophoblastic disease. In: Kirkham N, Lemoine NR (eds). Progress in pathology 3. Churchill Livingstone. New York 1997; 86–101.
Grayson W, Cooper K. Application of immunohistochemistry in the evaluation of neoplastic epithelial lesions of the uterine cervix and endometrium. Curr Diagn Pathol 2003; 9: 19–25.
Ismail SM. Gynaecological effects of Tamoxifen. J Clin Pathol 1999; 52: 83–88.
Kennedy MM, Manek S. The endometrium and hormonal manipulation: morphological features and review. CPD Bulletin Cellular Pathology 1998; 1(1): 15–18.
Loddenkemper C, Foss, HD, Dallenbach FE, Stein H. Recent advances in the histopathology of stromal tumours of the endometrium. Curr Diagn Pathol 2005; 11: 125–132.
Nucci MR. Application of biomarkers in the diagnosis and differential diagnosis of uterine and vulval mesenchymal tumours. Curr Diagn Pathol 2003; 9: 26–38.
Oliva E, Clement PB, Young RH. Mesenchymal tumours of the uterus; selected topics emphasizing diagnostic pitfalls. Curr Diagn Pathol 2002; 8: 268–282.
Oliva E, Young RH, Amin MB, Clement PB. An immunohistochemical analysis of endometrial stromal and smooth muscle tumors of the uterus. A study of 54 cases emphasizing the importance of using a panel because of overlap in immunoreactivity for individual antibodies. Am J Surg Pathol 2002; 26: 403–412.
Paradinas FJ. The histological diagnosis of hydatidiform moles. Curr Diagn Pathol 1994; 1: 24–31.
Paradinas FJ. The differential diagnosis of choriocarcinoma and placental site tumour. Curr Diagn Pathol 1998; 5: 93–101.
Prat J. Prognostic parameters of endometrial carcinoma. Hum Pathol 2004; 35: 649–662.
Scurry J, Patel K, Wells M. Gross examination of the uterine specimens. J Clin Pathol 1993; 46: 388–393.
Sebire NJ, Rees H. Diagnosis of gestational trophoblastic disease in early pregnancy. Curr Diagn Pathol 2002; 8: 430–440.
Sebire NJ, Rees HC, Peston D, Seckl MJ, Newlands ES, Fisher RA. $P57^{KIP2}$ immunohistochemical staining of gestational trophoblastic tumours does not identify the type of the causative pregnancy. Histopathology 2004; 45: 135–141.
Silverberg SG, Kurman RJ. Tumors of the uterine corpus and gestational trophoblastic disease. In: Atlas of tumor pathology. 3rd series. Fascicle 3. AFIP. Washington 1992.
Wilkinson N. Recent advances in mesenchymal lesions of the uterus. CPD Bulletin Cellular Pathology 1998; 1(1): 26–27.

Cervix

Al-Nafussi A. Tumours of the uterine cervix that can be underdiagnosed or misinterpreted. Curr Diagn Pathol 2003; 9: 56–70.
Arends MJ, Buckley CH, Wells M. Aetiology, pathogenesis, and pathology of cervical neoplasia. J Clin Pathol 1998; 51: 96–103.
Coleman DV, Evans DMD. Biopsy pathology and cytology of the cervix, 2nd edn. Arnold. London 1999.
Herbert A. BSCC terminology for cervical cytology: two or three tiers? Why not five, seven or even 14? Cytology 2004; 15: 245–251.

Histopathology reporting in cervical screening. NHSCSP Publication, No 10; April 1999.
Ioffe OB. Recent advances in the diagnosis and classification of endocervical glandular lesions. Curr Diagn Pathol 2004; 10: 404–412.
Kurian K, Al-Nafussi A. Relation of cervical glandular intraepithelial neoplasia to microinvasive and invasive adenocarcinoma of the uterine cervix: a study of 121 cases. J Clin Pathol 1999; 52: 112–117.
Kurman RJ, Norris HJ, Wilkinson EJ. Tumors of the cervix, vagina and vulva. Atlas of tumor pathology. 3rd series. Fascicle 4. AFIP. Washington 1992.
McCluggage WG. Endocervical glandular lesions: controversial aspects and ancillary techniques. J Clin Pathol 2003; 56: 164–173.
Rollason TP. Epithelial lesions of the endocervix. In: Kirkham N, Lemoine NR (eds). Progress in pathology 4. Churchill Livingstone. Edinburgh 1998; 179–199.
Young RH, Clements PB. Endocervical adenocarcinoma and its variants: their morphology and differential diagnosis. Histopathology 2002; 41: 185–207.

Vulva and vagina

Fox H, Wells M. Recent advances in the pathology of the vulva. Histopathology 2003; 42: 209–216.
Lage JM, Minamiguchi S, Richardson MS. Gestational trophoblastic diseases: update on new immunohistochemical findings. Curr Diagn Pathol 2003; 9: 1–10.
Nucci MR, Fletcher CDM. Vulvovaginal soft tissue tumours: update and review. Histopathology 2000; 36: 97–108.
Rollason TP. Recent advances in vulvar pathology. CPD Bulletin Cellular Pathology 1998; 1(1): 19–25.

UROLOGICAL CANCER

Bostwick DG, Eble JN (eds). Urological surgical pathology. Mosby. St Louis 1997.
Campbell MF, Walsh PC, Retik AB. Campbell's Urology, 8th edn. WB Saunders. Philadelphia 2002.
Eble JN, Sauter G, Epstein JI, Sesterhenn IA (eds). World Health Organisation Classification of Tumours. Pathology and Genetics. Tumours of the urinary system and male genital organs. IARC Press. Lyon 2004.
Ferry JA, Young RH. Malignant lymphoma of the genitourinary tract. Curr Diagn Pathol 1997; 4: 145–169.
Petersen RO. Urologic pathology, 2nd edn. Lippincott. Philadelphia 1992.

Kidney

Amin MB, Amin MB, Tamboli P, Javidan J, Stricker H, Venturina MD-P, Deshpande A, Menon M. Prognostic impact of histologic subtyping of adult renal epithelial neoplasms. An experience of 405 cases. Am J Surg Pathol 2002; 26: 281–291.
Bonsib SM. The renal sinus is the principal invasive pathway. A prospective study of 100 renal cell carcinomas. Am J Surg Pathol 2004; 28: 1594–1600.
Davies DR. The reporting of renal cell tumours. CPD Bulletin Cellular Pathology 2000; 2: 40–45.
Fleming S. Classification of renal epithelial neoplasms. Curr Diagn Pathol 2002; 8: 34–44.
Fleming S, Griffiths DFR. Nephrectomy for renal tumour; dissection guide and dataset. ACP Best practice no 180. J Clin Pathol 2005; 58: 7–14.
Fleming S. Recently recognized epithelial tumours of the kidney. Curr Diagn Pathol; 2005; 11: 162–169.

Fuhrman SA, Lasky LC, Limas C. Prognostic significance of morphologic parameters in renal cell carcinoma. Am J Surg Pathol 1982; 6: 655–663.
Griffiths DFR, Vujanic GM. Cystic lesions of the kidney-selected topics. Curr Diagn Pathol 2002; 8: 94–101.
Griffiths DFR, Nind N, O'Brien CJ, Rashid M, Verghese A. Evaluation of a protocol for examining nephrectomy specimens with renal cell carcinoma. J Clin Pathol 2003; 56: 374–377.
Kovacs G, Akhtar M, Beckwith BJ, Bugert P, Cooper CJ, Delahunt B. The Heidelberg classification of renal tumours. J Pathol 1997; 183: 131–133.
Langner C, Ratschek M, Rehak P, Schips L, Zigeuner R. CD10 is a diagnostic and prognostic marker in renal malignancies. Histopathology 2004; 40: 563–467.
Mathers C, Pollock AM, Marsh C, O'Donnell M. Cytokeratin 7: a useful adjunct in the diagnosis of chromophobe renal cell carcinoma. Histopathology 2002; 40: 563–567.
Murphy WM, Grignon DJ, Perlman EJ. Tumors of the kidney, bladder and related urinary structures. Atlas of tumor pathology. 4th series. Fascicle 1. AFIP. Washington 2004.
Olgae S, Mazumdar M, Dalbagni G, Reuter VE. Urothelial carcinoma of the renal pelvis. A clinicopathologic study of 130 cases. Am J Surg Pathol 2004; 28: 1545–1552.
Pan C-C, Chen PC-H, Ho DM-T. The diagnostic utility of MOC31, BerEP4, RCC marker and CD10 in the classification of renal cell carcinoma and renal oncocytoma: an immunohistochemical analysis of 328 cases. Histopathology 2004; 45: 452–459.
Renshaw AA, Richie JP. Subtypes of renal cell carcinoma. Different onset and sites of metastatic disease. Am J Clin Pathol 1999; 111: 539–543.
Renshaw AA. Subclassification of renal cell neoplasms: an update for the practising pathologist. Histopathology 2002; 41: 283–300.
Thomas DH, Verghese A, Kynaston HG, Griffiths DFR. Analysis of the prognostic implications of different tumour margin types in renal cell carcinoma. Histopathology 2003; 43: 374–380.
Venturina MD-P, Moch H, Amin M, Tamboli P, Hailemarian S, Mitatsch M, Javidan J, Stricker H, Ro JY, Amin MB. Sarcomatoid differentiation in renal cell carcinoma. A study of 101 cases. Am J Surg Pathol 2001; 25: 275–284.

Urinary bladder

Ansell D. Reporting in urothelial tumours. CPD Bulletin Cellular Pathology 2000; 2: 22–24.
Bates AW, Baithun SI. Secondary neoplasms of the bladder are histological mimics of nontransitional cell primary tumours: clinicopathological and histological features of 282 cases. Histopathology 2000; 36: 32–40.
Cheng L, Cheville JC, Neumann RM, Bostwick DG. Natural history of urothelial dysplasia of the bladder. Am J Surg Pathol 1999; 23: 443–447.
Epstein JI, Amin MB, Reuter VR, Mostofi FH and the Bladder Consensus Conference Committee. The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. Am J Surg Pathol 1998; 22: 1435–1448.
Fleischmann A, Thalmann GN, Markwalder R, Studer UE. Prognostic implications of extracapsular extension of pelvic lymph node metastases in urothelial carcinoma of the bladder. Am J Surg Pathol 2005; 29: 89–95.

Harnden P, Parkinson MC. Transitional cell carcinoma of the bladder: diagnosis and prognosis. Curr Diagn Pathol 1996; 3: 109–121.
Harnden P. Mimics of carcinoma and problematic lesions in the urinary bladder. CPD Bulletin Cellular Pathology 2000; 2: 25–28.
Harnden P. Transitional cell tumours of the bladder: classification and diagnostic pitfalls. Curr Diagn Pathol 2002; 8: 76–82.
Lopez-Beltran A, Luque RJ, Mazzucchelli R, Scarpelli M, Montironi R. Changes produced in the urothelium by traditional and newer therapeutic procedures for bladder cancer. J Clin Pathol 2002; 55: 641–647.
Levine T. Urine cytology of malignancy and diagnostic pitfalls. CPD Bulletin Cellular Pathology 2000; 2: 8–12.
Magi-Galluzzi C, Epstein JI. Urothelial papilloma of the bladder. A review of 34 de novo cases. Am J Surg Pathol 2004; 28: 1615–1620.
McKenney JK, Gomez JA, Desai S, Lee MW, Amin MB. Morphologic expressions of urothelial carcinoma in-situ. A detailed evaluation of its patterns with emphasis on carcinoma in-situ with microinvasion. Am J Surg Pathol 2001; 28: 356–362.
Montironi R, Lopez-Beltran A, Mazzucchelli R, Bostwick DG. Classification and grading of the non-invasive urothelial neoplasms: recent advances and controversies. J Clin Pathol 2003; 56: 91–95.
Ramos D, López-Guerrero JA, Navarro S, Llombart-Bosch A. Prognostic markers in low-grade papillary urothelial neoplasms of the urinary bladder. Curr Diagn Pathol 2005; 11: 141–150.
Varma M, Morgan M, Amin MB, Wozniak S, Jasani B. High molecular weight cytokeratin antibody (clone 34βE12): a sensitive marker for differentiation of high-grade invasive urothelial carcinoma from prostate cancer. Histopathology 2003; 42: 167–172.
Webb JN. Aspects of tumours of the urinary bladder and prostate gland. In: Anthony PP, MacSween RNM (eds). Recent advances in histopathology 15. Churchill Livingstone. Edinburgh 1992; 157–176.
Young RH (ed). Pathology of the urinary bladder. Churchill Livingstone. New York 1989.

Prostate

Ali TZ, Epstein JI. Perineural involvement by benign prostatic glands on needle biopsy. Am J Surg Pathol 2005; 29: 1159–1163.
Bostwick DG, Brawer MK. Prostatic intraepithelial neoplasia and early invasion in prostate cancer. Cancer 1987; 55: 788–794.
Bostwick DG, Dundore PA. Biopsy pathology of the prostate. Chapman and Hall Medical. London 1997.
Egevad L, Allsbrook WC, Epstein JI. Gleason grading of prostatic carcinoma. http://pathology2.jhu.edu/gleason
Epstein JI. The evaluation of radical prostatectomy specimens. Therapeutic and prognostic implications. Pathol Ann 1991; 159–210.
Epstein JI, Allsbrook WC, Amin MB, Egevad LL and the ISUP Grading Committee. The 2005 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma. Am J Surg Pathol 2005; 29: 1228–1242.
Evans AJ. α-Methylacyl Co A racemase (P504S): overview and potential in diagnostic pathology as applied to prostate needle biopsies. J Clin Pathol 2003; 56: 892–897.
Foster CA, Sakr WA. Proliferative lesions of the prostate that mimic carcinoma. Curr Diagn Pathol 2001; 7: 194–212.

Gleason D. Histologic grading and clinical staging of prostatic carcinoma. In: Tannenbaum M (ed). Urologic Pathology. The Prostate. Lea and Febiger. Philadelphia 1977; 171–198.
Gleason DF. Histologic grading of prostate cancer; a perspective. Hum Pathol 1992; 23: 273–279.
McWilliam LJ, Roberts ISD, Davies DR. Problems in grading and staging prostatic carcinoma. Curr Diagn Pathol 2002; 8: 65–75.
Montironi R, Schulman CC. Pathological changes in prostate lesions after androgen manipulation. J Clin Pathol 1998; 51: 5–12.
Montironi R, Thompson D, Bartels PH. Premalignant lesions of the prostate. In: Lowe DG, Underwood JCE (eds). Recent advances in histopathology 18. Churchill Livingstone. Edinburgh 1999; 147–172.
Montironi R, Mazzucchelli R, Algaba F, Lopez-Beltram A. Morphologic identification of the patterns of prostatic intraepithelial neoplasia and their importance. J Clin Pathol 2000; 53: 655–665.
Montironi R, Mazzucchelli R, Stramazotti D, Scarpelli M, López-Beltram A, Bostwick DG. Basal cell hyperplasia and basal cell carcinoma of the prostate: a comprehensive view and discussion of a case with c-erbB-2 expression. J Clin Pathol 2005; 58: 290–296.
Parkinson MC. Pre-neoplastic lesions of the prostate. Histopathology 1995; 27: 301–311.
Parkinson MC. Prostatic carcinoma: prognostic factor interpretation in core biopsy and radical specimens. CPD Bulletin Cellular Pathology 2000; 2: 17–21.
Skinnider BF, Oliva E, Young RH, Amin MB. Expression of α-Methylacyl-Co A racemase (P404S) in nephrogenic adenoma. A significant immunohistochemical pitfall compounding the differential diagnosis with prostatic adenocarcinoma. Am J Surg Pathol 2004; 28: 701–705.
Van der Kwast Th H, Lopes C, Santonja C, Pihl C-G, Neetens I, Martikainen P, Di Lollo S, Bubendolf L, Hoedemaeker RF, members of the pathology committee of the European Randomised Study of Screening for Prostate Cancer (ERSPC). Guidelines for processing and reporting of prostatic needle biopsies. J Clin Pathol 2003; 56: 336–340.
Vargas SO, Jiroutek M, Welch WR, Nucci MR, D'Amico AV, Renshaw AA. Perineural invasion in prostate needle biopsy specimens. Correlation with extraprostatic extension at resection. Am J Clin Pathol 1999; 111: 223–228.
Young RH, Srigley JR, Amin MB, Ulbright TM, Cubilla A. Tumors of the prostate gland, seminal vesicle, male urethra and penis. Altas of Tumour Pathology. Series 3. Fascicle 28. AFIP. Washington 2000.

Testis

Ansell D. The reporting of testicular tumours. Curr Diagn Pathol 2000; 6: 192–199.
Attanoos RL, Gibbs AR. Primary malignant gonadal mesotheliomas and asbestos. Histopathology 2000; 37: 150–159.
Berney DM, Lee A, Randle SJ, Jordans S, Shamash J, Oliver RTD. The frequency of intratubular embryonal carcinoma: implications of the pathogenesis of germ cell tumours. Histopathology 2004; 45: 155–161.
Berney DM. A practical approach to the reporting of germ cell tumours of the testis. Curr Diagn Pathol 2005; 11: 151–161.
Cullen MH, Stenning SP, Parkinson MC, Fossa SD, Kaye SB, Horwich AH. Short-course adjuvant chemotherapy in high-risk stage I nonseminomatous germ cell tumours of the testis. A Medical Research Council report. J Clin Oncol 1996; 14: 1106–1113.

Fisher C. Paratesticular tumours and tumour-like lesions. CPD Bulletin Cellular Pathology 2000; 2: 13–16.
Grigor KM. Germ cell tumours of the testis. In: Anthony PP, MacSween RNM (eds). Recent advances in histopathology 15. Churchill Livingstone. Edinburgh 1992; 177–194.
Grigor KM. How to report a testicular tumour. CPD Bulletin Cellular Pathology 2000; 2: 36–39.
International Germ Cell Cancer Collaborative Group. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. J Clin Oncol 1997; 15: 594–603.
Parkinson MC. The role of the histopathologist in the management of testicular germ cell tumours in adults. Histopathology 2001; 38: 188–194.
Pugh RCB (ed). Pathology of the testis. Blackwell Scientific. Oxford 1976.
Read G, Stenning SP, Cullen MH, Parkinson MC, Horwich A, Kaye SB, Cook PA. Medical Research Council prospective study of surveillance for stage I testicular teratoma. MRC Testicular Tumour Working Party. J Clin Oncol 1992; 10: 1762–1768.
Shanks JH, Iczkowski KA. Non-germ cell tumours of the testis. Curr Diagn Pathol 2002; 8: 83–93.
Stenning SP, Parkinson MC, Fisher C, Mead GM, Cook PA, Fossa SD et al. Post-chemotherapy residual masses in germ cell tumour patients; content, clinical features and prognosis. Medical Research Council Testicular Tumour Working Party. Cancer 1998; 83: 1409–1419.
Theaker JM, Mead GM. Diagnostic pitfalls in the histological diagnosis of testicular germ cell tumours. Curr Diagn Pathol 2004; 10: 220–228.
Ulbright TM, Amin MB, Young RH. Tumors of the testis, adnexa, spermatic cord, and scrotum. Atlas of tumor pathology. 3rd series. Fascicle 25. AFIP. Washington 1999.
Young RH, Talerman A. Testicular tumours other than germ cell tumours. Semin Diagn Pathol 1987; 4: 342–360.

LYMPH NODE CANCER

Bain BJ, Clark DM, Lampert IA. Bone marrow pathology. Blackwell Scientific. Oxford 1992.
Banerjee SS, Verma S, Shanks JH. Morphological variants of plasma cell tumours. Histopathology 2004; 44: 2–8.
Buley ID. Cytology of metastatic neoplasms in lymph nodes. In: Lowe DG, Underwood JCE (eds). Recent advances in histopathology 18. Churchill Livingstone. Edinburgh 1999; 116–118.
Chan JKC. Tumours of the lymphoreticular system; including spleen and thymus. In: Fletcher CDM (ed). Diagnostic Histopathology of Tumours, 2nd edn. Volume 2. Harcourt. London 2000; 1099–1245.
Chan JKC, Banks PM, Cleary ML, Delsol G, de Wolf-Peters C, Falini B, Gatter KC, Grogan TM, Harris NL, Isaacson PG, Jaffe ES, Knowles DM, Mason DY, Müller-Hermelink HK, Pileri SA, Piris MA, Ralfkiaer E, Stein H, Warnke RA. A proposal for classification of lymphoid neoplasms (by the International Lymphoma Study Group). Histopathology 1994; 25: 517–536.
DeLeval L, Harris NL. Variability in immunophenotype in diffuse large B-cell lymphoma and its significance. Histopathology 2003; 43: 509–528.
Extranodal hematopoietic/lymphoid disorders. Pathology patterns. Am J Clin Pathol 1999; 111(Suppl. 1): S1–S152.
Gatter K, Brown D. An illustrated guide to bone marrow diagnosis. Blackwell Scientific. Oxford 1997.

Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Delabie J, Ott G, Müller-Hermelink HK, Campo E, Braziel RM, Jaffe ES, Pan Z, Farinha P, Smith LM, Falini B, Banham AH, Rosenwald A, Staudt LM, Connors JM, Armitage JO, Chan WC. Confirmation of the molecular classification of diffuse large B-cell lymphoma immunohistochemistry using a tissue microarray. Blood 2004: 103: 275–282.

Harris NL, Jaffe ES, Diebold J, Flandrin G, Müller-Hermelink HK, Vardiman J, Lister TA, Bloomfield CD. The World Health Organization classification of neoplastic diseases of the haemopoietic and lymphoid tissues: report of the clinical advisory committee meeting, Airlie House, Virginia, November 1997. Histopathology 2000; 36: 69–87.

Harris NL, Jaffe ES, Stein H et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994; 84: 1361–1392.

Hermans J, Krol AD, van Groningen K et al. International Prognostic Index for aggressive non-Hodgkin's lymphoma is valid for all malignancy grades. Blood 1995; 86: 1460–1463.

Hopwood P, Crawford DH. The role of EBV in post-transplant malignancies: a review. J Clin Pathol 2000; 53: 248–254.

Isaacson PG, Norton AJ. Extranodal lymphomas. Churchill Livingstone. Edinburgh 1994.

Jack A. Clinically indolent lymphomas presenting in lymph nodes. CPD Bulletin Cellular Pathology 2002; 4: 9–12.

Jaffe ES, Harris NL, Stein H, Vardiman J (eds). World Health Organisation Classification of Tumours, Pathology and Genetics. Tumours of the Haematopoietic and Lymphoid Tissues. IARC Press. Lyon 2001.

Kocjan C. Cytological and molecular diagnosis of lymphoma. ACP Best Practice No 185. J Clin Pathol 2005; 58: 561–567.

Kluin PM, Feller A, Gaulard P, Jaffe ES, Meijer CJLM, Müller-Hermelink HK, Pileri S. Peripheral T/NK-cell lymphoma: a report of the IXth workhop of the European Association for haematopathology. Histopathology 2001; 38: 250–270.

Lauder I. T-cell malignant lymphomas. In: Anthony PP, MacSween RNM (eds). Recent advances in histopathology 15. Churchill Livingstone. Edinburgh 1992; 93–112.

Leoncini L, Delsol G, Gascoyne RD, Harris NL, Pileri SA, Piris MA, Stein H. Aggressive B-cell lymphomas: a review based on the workshop of the XI meeting of the European Association for Haematopathology. Histopathology 2005; 46: 241–255.

Maes B, De Wolf-Peeters C. Marginal zone cell lymphoma—an update on recent advances. Histopathology 2002: 40: 117–126.

MacLennan KA. Recent advances in the pathology of Hodgkin's lymphoma. CPD Bulletin Cellular Pathology 2002; 4: 25–28.

Müller-Hermelink HK, Zettl A, Pfeifer W, Ott G. Pathology of lymphoma progression. Histopathology 2001; 38: 285–306.

Pileri SA, Grogan TM, Harris NL et al. Tumours of histiocytes and accessory dendritic cells: an immunohistochemical approach to classification from the International Lymphoma Study Group based on 61 cases. Histopathology 2002; 41: 1–29.

Pileri SA, Dirnhofer S, Went PH, Ascani S, Sabattini E, Marafioti T, Tzankov A, Leoncini L, Falini B, Zinizani PL. Diffuse large B-cell lymphoma: one or more entities? Present controversies and possible look for its subclassification. Histopathology 2002; 41: 482–509.

Ramsay A. High-grade lymphomas in lymph nodes. CPD Bulletin Cellular Pathology. 2002; 4: 18–24.
Sagaert X, De Wolf-Peeters C. Anaplastic large cell lymphoma. Curr Diagn Pathol 2003; 9: 252–258.
Stansfeld AG, d'Ardenne AJ (eds). Lymph node biopsy interpretation, 2nd edn. Churchill Livingstone. Edinburgh 1992.
Stevenson SK, Wright DH. Hodgkin's disease and immunoglobulin genetics. In: Kirkham N, Lemoine NR (eds). Progress in pathology 4. Churchill Livingstone. Edinburgh 1998; 99–111.
Strauchen JA. Diagnostic histopathology of the lymph node. Oxford University Press. Oxford 1998.
Swerdlow SH. Post-transplant lymphoproliferative disorders: a working classification. Curr Diagn Pathol 1997; 4: 28–35.
Taylor CR. Hodgkin's disease is a non-Hodgkin's lymphoma. Hum Pathol 2005; 36: 1–4.
The Non-Hodgkin's Lymphoma Classification Project. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. Blood 1997; 89: 3909–3918.
Warnke RA, Weiss LM, Chan JKC, Cleary ML, Dorfman RF. Tumors of the lymph nodes and spleen. Atlas of tumor pathology. 3rd series. Fascicle 14. AFIP. Washington 1995.
Wilkins BS, Wright DH. Illustrated pathology of the spleen. Cambridge University Press. Cambridge 2000.
Wilkins B (ed). Mini-symposium: haematolymphoid pathology. Curr Diagn Pathol 2004; 10: 344–393.
Wotherspoon AC, Hasserjian RP. Immunophenotyping in the differential diagnosis of histologically low grade B-cell lymphoma. Curr Diagn Pathol 2000; 6: 55–63.
Wright D, McKeever P, Carter R. Childhood non-Hodgkin's lymphomas in the United Kingdom: findings from the UK Children's Cancer Study Group. J Clin Pathol 1997; 50: 128–134.

BONE AND SOFT TISSUE CANCER

Al-Nafussi A. Practical morphological approach to the diagnosis and differential diagnosis of soft tissue sarcomas. Curr Diagn Pathol 2002; 8: 395–411.
Bullough PG. Orthopaedic Pathology, 4th edn. Mosby Wolfe. St Louis 1998.
Coffin CM, Lowichik A, Zhou H. Treatment effects in paediatric soft tissue and bone tumors. Am J Clin Pathol 2005; 123: 75–90.
Coindre J-M, Trojani M, Contesso G, David M, Rouesse J, Bui NB, Bodaert A, de Mascarel I, de Mascarel A, Goussot JF. Reproducibility of a histopathologic grading system for adult soft tissue sarcoma. Cancer 1986; 58: 306–309.
Coindre JM. Immunohistochemistry in the diagnosis of soft tissue tumours. Histopathology 2003; 43: 1–16.
Costa J, Wesley RA, Glatstein E, Rosenberg SA. The grading of soft tissue sarcomas. Results of a clinicohistopathologic correlation in a series of 163 cases. Cancer 1984; 53: 530–541.
Dako. Immunohistochemistry in the Diagnosis of Soft Tissue Sarcomas. DAKO. Glostrup 1999.
Enzinger FM, Weiss SW. Soft Tissue Tumours, 4th edn. Mosby-Wolfe. St Louis 2000.
Fechner RE, Mills SE. Tumours of the Bones and Joints. 3rd series. Fascicle 8. AFIP. Washington 1993.

Fletcher CDM. The evolving classification of soft tissue tumours: an update based on the new WHO classification. Histopathology 2006; 48: 3–12.
Fletcher CDM, Unni KK, Mertens F. World Health Organisation Classification of Tumours. Pathology and Genetics. Tumours of soft tissue and bone. IARC Press. Lyon 2002.
Goodlad JR, Fletcher CDM. Recent developments in soft tissue tumours. Histopathology 1995; 27: 103–120.
Graadt van Roggen JF, Bovee JVMG, Morreau J, Hogendoorn PCW. Diagnostic and prognostic implications of the unfolding molecular biology of bone and soft tissue tumours. J Clin Pathol 1999; 52: 481–489.
Graadt van Roggen JF. The histopathological grading of soft tissue tumours: current concepts. Curr Diagn Pathol 2001; 7: 1–7.
Guillou L, Fletcher CDM. Newer entities in soft tissue tumours. Curr Diagn Pathol 1997; 4: 210–221.
Hahn HP, Fletcher CDM. The role of cytogenetics and molecular genetics in soft tissue tumour diagnosis—a realistic approach. Curr Diagn Pathol 2005; 11: 361–370.
Holloway P, Kay E, Leader M. Myxoid tumours: a guide to the morphological and immunohistochemical assessment of soft tissue myxoid lesions encountered in general surgical pathology. Curr Diagn Pathol 2005; 11: 411–425.
Kempson RL, Fletcher CDM, Evans HL, Hendrickson MR, Sibley RK. Tumours of the Soft Tissues. 3rd series: Fascicle 30. AFIP. Washington 2001.
Malone M. Soft tissue tumours in childhood. Histopathology 1993; 23: 203–216.
Mentzel T, Fletcher CDM. Recent advances in soft tissue tumor diagnosis. Am J Clin Pathol 1998; 110: 660–670.
Pfeifer JD, Hill DA, O'Sullivan MJ, Dehner LP. Diagnostic gold standard for soft tissue tumours: morphology or molecular genetics? Histopathology 2000; 37: 485–500.
Pringle JAS. Osteosarcoma: the experiences of a specialist unit. Curr Diagn Pathol 1996; 3: 127–136.
Salzer-Kuntschik M, Delling G, Beron G, Sigmund R. Morphological grades of regression in osteosarcoma after polychemotherapy—Study Coss 80. J Cancer Res Clin Pract 1993: 106, Suppl: 21–24.
Wijnaendts LCD, van der Linden JC, van Unnick AJM, Voûte PA, Meijer CJLM. Rhabdomyosarcoma: results of a Dutch unicenter study. Curr Diagn Pathol 1996; 3: 137–142.

OPHTHALMIC CANCER

Callender GR. Malignant melanocytic tumours of the eye: a study of histologic types in 111 cases. Trans Am Acad Ophthalmol Otolaryngol 1931; 36: 131–142.
Campbell RJ. Histological typing of tumours of the eye and its adnexa, 2nd edn. WHO: International histological classification of tumours. Springer. Berlin Heidelberg New York 1998.
Lee WR. Ophthalmic histopathology. Springer-Verlag. London 1993.
McLean IW, Foster WD, Zimmerman LE. Uveal melanoma: location, size, cell type and enucleation as risk factors in metastasis. Hum Pathol 1982; 13: 123–132.
McLean IW, Burnier MN, Zimmerman LE, Jakobiec FA. Tumors of the eye and ocular adnexa. Atlas of tumor pathology. 3rd series. Fascicle 12. AFIP. Washington 1994.
Shields CL, Shields JA, Baez KA, Cater J, De Potter PV. Optic nerve invasion of retinoblastoma: metastatic potential and clinical risk factors. Cancer 1994; 73: 692–698.

Index

Page numbers in italics refer to figures or tables.