Clinical Pathology of
UROLOGIC TUMORS

Edited by

GREGOR MIKUZ
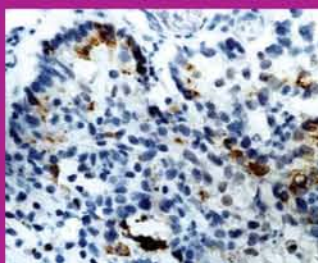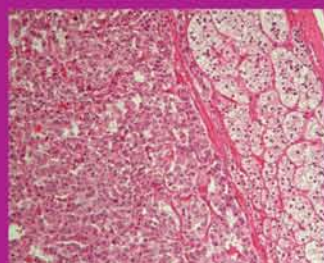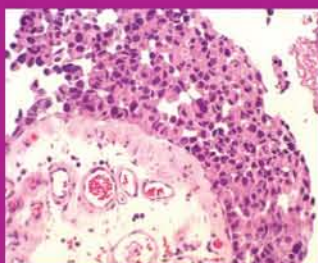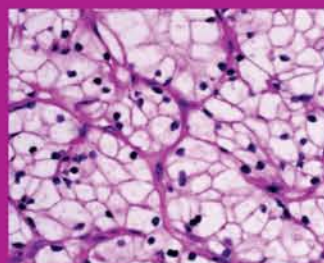
informa
healthcare

Clinical Pathology of Urologic Tumors

Clinical Pathology of Urologic Tumors

Edited by

Gregor Mikuz MD FRCPath
Professor of Pathology
Director, Institute of Pathology
Medical University Innsbruck
Innsbruck
Austria

informa
healthcare

Although every effort has been made to ensure that all owners of copyright material have been acknowledged in this publication, we would be glad to acknowledge in subsequent reprints or editions any omissions brought to our attention.

Although every effort has been made to ensure that drug doses and other information are presented accurately in this publication, the ultimate responsibility rests with the prescribing physician. Neither the publishers nor the authors can be held responsible for errors or for any consequences arising from the use of information contained herein. For detailed prescribing information or instructions on the use of any product or procedure discussed herein, please consult the prescribing information or instructional material issued by the manufacturer.

Contents

Contributors

Matteo Brunelli MD
Assistant Professor
Department of Pathology
University of Verona
Italy

Liang Cheng MD
Departments of Pathology and Laboratory Medicine
Indiana University School of Medicine
Indianapolis
USA

Maurizio Colecchia MD
Dipartimento di Patologia
Instituto Nazionale per lo Studio e la Cura dei Tumori
Milano
Italy

Antonio L Cubilla MD
Professor of Pathology
Facultad de Ciencias Medicas
University Nacional de Asunción
Director Instituto de Patología e Investigacion
Asunción
Paraguay

Vincenzo Ficarro MD
Associate Professor
Department of Urology
University of Padua
Italy

Stefano Gobbo MD
Fellow
Department of Pathology
University of Verona
Italy

Antonio Lopez-Beltran MD PhD
Department of Pathology
Reina Sofia University Hospital and Cordoba University
  Medical School
Cordoba
Spain

Guido Martignoni MD
Associate Professor
Department of Pathology
University of Verona
Italy

Roberta Mazzucchelli MD PhD
Institute of Pathological Anatomy and Histopathology
Polytechnic University of the Marche Region
Ancona
Italy

Gregor Mikuz MD FRCPath
Professor of Pathology
Medical University Innsbruck
Innsbruck
Austria

Rodolfo Montironi MD FRCPath
Institute of Pathological Anatomy and Histopathology
Polytechnic University of the Marche Region
Ancona
Italy

Maurizio Pea MD
Consultant Pathologist
Department of Pathology
University of Verona
Italy

Marina Scarpelli MD
Section of Pathological Anatomy and Histopathology
Polytechnic University of the Marche Region
Ancona
Italy

Regina Tardanico MD
Consultant Pathologist
Department of Pathology
University of Brescia
Italy

Elsa F Velazquez MD
Assistant Professor of Pathology
Harvard Medical School
Associate Pathologist
Brigham & Women's Hospital
Boston, MA
USA

Alfredo Vidal-Jimenez
Unit of Anatomic Pathology
Cordoba University Medical School and
  Reina Sofia University Hospital
Cordoba
Spain

Preface

Since 1890, when in Paris urology became a separate course of study from general surgery, this speciality has developed into a field of medicine in which science, technical developments, diagnostic procedures, and invasive as well as non-invasive therapeutic measures have reached their highest levels. Urologic admissions and surgical procedures are among the most frequently performed interventions in current hospital care. In 1992, a century later, pathologists dealing with urologic problems founded an international society of this subspecialization. Long before, however, outstanding pathologists on both sides of the Atlantic devoted their lives to the study of urologic disease, mainly tumors arising in the genitourinary system. Pathologists and urologists have learned in recent decades to discuss very open-mindedly the common issues and have achieved in many institutions an exemplary degree of reciprocal understanding. The cooperation is not limited to daily diagnostics but rather, extends to common scientific approaches and work.

The efforts of the uropathologists led to new generally accepted WHO classifications of urologic tumors, which are indispensable for therapy planning and for the comparison of the results among different institutions. Many of the new morphologic tumor classifications are already based on knowledge achieved through new methods, which allow the pathologists to analyze chromosomes and genes as well as their aberrations and mutations even in the 'dead' cells of paraffin-embedded tissue. Alterations of the tumor cell genome are entering into daily pathologic routines and will in the near future permit a more individual therapeutic approach. Nevertheless, at present surgery is still the first and most important procedure in the basic therapy of urologic tumors and biopsy the most important diagnostic approach (1 million prostate biopsies worldwide!). Even for chemotherapy treatment, morphology is used for the choice of drugs and for the assessment of their effectiveness.

This book is not intended as a 'workbench' book or an atlas for pathologists – there are numerous outstanding publications dealing with the pathologic diagnostic of single genitourinary organs. Its objective is to give urologists and other interested clinicians an overview of the morphology of the tumors of the genitourinary system. The international classifications, grading, and staging procedures which are included, as well as the rules for sampling and handling of the biopsy and surgical specimens, should permit a better understanding of the morphologic assessment of the tumor diseases. The uses of modern morphologic techniques for differential diagnostic purposes are presented in order to show clinicians what the current possibilities and limits of a pathologic diagnosis are.

A book written by many authors has both weaknesses and strengths. We take into account that the single chapters differ in style, which may disturb some readers. Yet we regard this also as a strength because the very personal approach of the authors reflects their longstanding diagnostic and scientific careers, which have undergone much scrutiny and testing at international congresses and classification committees, and in scientific papers and books. Moreover, tumors of the genitourinary system cannot be compared with those of other systems. Gastrointestinal tract tumors, for example, have a very similar morphology and prognostic assessment observes the same rules for all single segments. Prostate and testis tumors do not have anything in common except the gender of the patients. The bare history of the grading of bladder cancer, which has changed three times in the last 10 years, would deserve its own chapter. Kidney tumors are the first example of a classification based on the karyotype of the tumor. Tumors of the adrenals are still a diagnostic problem because they are so rare. Last but not least, the penis carcinoma, which is practically unknown in Europe and the US, requires an expert who confronts this problem daily.

On behalf of all the authors, I venture to extend a debt of gratitude to all those anonymous colleagues and friends who with their comments and questions have enlarged and enriched our experience. I also thank all our partners who over the last few months spent their evenings alone, even more frequently than usual.

Gregor Mikuz

Section 1

Renal tumors

Guido Martignoni, Regina Tardanico, Maurizio Pea, Matteo Brunelli, Stefano Gobbo, and Vincenzo Ficarra

Part 1

Epidemiology, etiology, and clinical history

Renal cell carcinoma represents on average over 90% of all malignancies of the kidney that occur in adults in both sexes. Renal cell cancer is the seventh leading malignant condition among men and the twelfth among women, accounting for 2.6% of all cancers. A 1.6:1.0 male predominance exists and the peak incidence is in the sixth and seventh decades. About 2% of cases of renal cancer are associated with inherited syndromes. The American Cancer Society estimated 38 890 (24 650 in males and 14 240 in females) new renal cancers and 12 840 (8 130 males and 4 710 females) deaths in the United States during 2006.[1]

Tobacco smoking is a major cause of kidney cancer and accounts for at least 39% of all cases in males. Exposure to carcinogenic arsenic compounds in industrial processes or through drinking water increases the risk of renal cancer by 30%. Several other environmental chemicals have been addressed as possible carcinogens, including asbestos, cadmium, some organic solvents, pesticides, and fungal toxins. Estrogens could be involved in the mechanism that induces renal cell carcinoma in overweight and obese individuals.[2] The incidence of renal cell carcinoma in obese people is double that of normal individuals and it is also significantly increased in people with a history of blood hypertension. Other exposures that have been addressed are a family history of kidney cancer, birth weight, low consumption of fruits and vegetables, and the use of antihypertensive drugs other than diuretics.[3,4]

The classic symptomatic presentation includes the triad hematuria, flank pain, and palpable abdominal mass. Other common presenting features may be not specific, such as fatigue, weight loss, and anemia. Currently only a few patients present in this manner and roughly half of the cases are now detected because a renal mass is incidentally identified on ultrasound (Figure 1.1) or computed tomography (CT) scan examination (Figure 1.2). It has been reported that the percentage of incidental renal cancers increased from 17% between 1976 and 1980, rising to 58% over recent years.[5] Moreover, Patard et al proposed classifying patients with renal cancer according to the mode of presentation: S1, symptomatic; S2, patients with local symptoms; and S3, patients with systemic symptoms.[6] Elevation of the erythrocyte sedimentation rate occurs in approximately 50% of cases. Renal cell carcinoma may induce paraneoplastic endocrine syndromes, including pseudohyperparathyroidism, erythrocytosis, hypertension, and gynecomastia. Hypercalcemia without bone metastases occurs in approximately 10% of patients and in nearly 20% of patients with disseminated carcinoma. In about 66% of patients, erythropoietin concentration is elevated. Renal cell carcinoma also is known for presenting as metastatic carcinoma of an unknown primary, sometimes in unusual sites. Radiologic criteria established by Bosniak assist the management of renal masses.[7,8]

Ultrasonography is useful for detecting renal lesions and if it is not diagnostic of a simple cyst, CT before and after intravenous contrast is required. Plain CT may confirm a benign diagnosis by identifying fat in angiomyolipoma. Lesions without enhancement require nothing further, but those with enhancement require follow-up at 6 months, 1 year, and then annually.[9–16]

Figure 1.1
Ultrasonography: small cortical renal nodule.
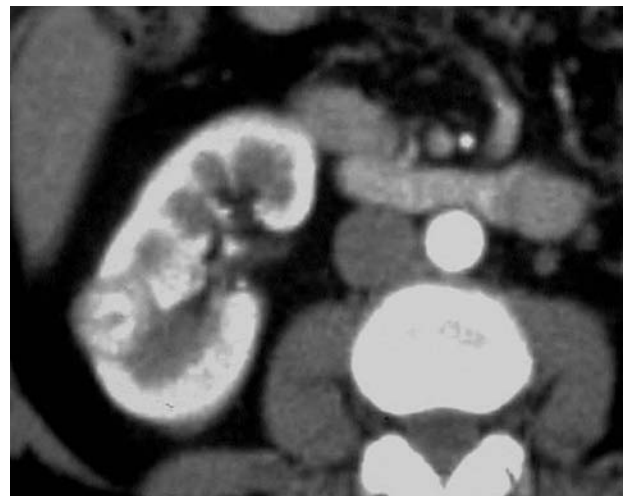
Figure 1.2
CT scan after intravenous contrast showing a renal cortical mass.

Part 2

Pathology

The neoplasms of the kidney are classified by using the World Health Organization (WHO) 2004 system,[17] which represents the evolution of the 1997 Consensus Classifications of Heidelberg and Rochester.[18,19] The WHO 2004 system defines tumor subtypes with distinct histopathologic features, clinical behavior, and genetic alterations. This classification is critical for clinical management of renal tumors and emergence of molecular therapies directed at tumor gene activity.[20] Both benign and malignant neoplasms are listed as well as a diagnostic category named 'renal cell carcinoma, unclassified', to which can be assigned tumors which do not fit into any of the established categories (Figure 1.3).

In the next paragraphs we will describe how to handle the specimens from patients with renal tumors, the macroscopic and histologic features of the renal neoplasms, and the most important

Renal cell neoplasms
Clear cell renal cell carcinoma
Multilocular clear cell renal cell carcinoma
Papillary renal cell carcinoma
Chromophobe renal cell carcinoma
Carcinoma of the collecting ducts of Bellini
Renal medullary carcinoma
Xp11 translocation carcinomas
Carcinoma associated with neuroblastoma
Mucinous tubular and spindle cell carcinoma
Renal cell carcinoma, unclassified
Papillary adenoma
Oncocytoma

Metanephric neoplasms
Metanephric adenoma
Metanephric adenofibroma
Metanephric stromal tumor

Nephroblastic neoplasms
Nephrogenic rests
Nephroblastoma
Cystic partially differentiated nephroblastoma

Mesenchymal neoplasms
Clear cell sarcoma
Rhabdoid tumor
Congenital mesoblastic nephroma
Ossifying renal tumor of infants
Leiomyosarcoma
Angiosarcoma

Rhabdomyosarcoma
Malignant fibrous histiocytoma
Hemangiopericytoma
Osteosarcoma
Angiomyolipoma
Epithelioid angiomyolipoma
Leiomyoma
Hemangioma
Lymphangioma
Juxtaglomerular cell tumor
Renomedullary interstitial cell tumor
Schwannoma
Solitary fibrous tumor

Mixed mesenchymal and epithelial neoplasms
Cystic nephroma
Mixed epithelial and stromal tumor
Synovial sarcoma

Neuroendocrine neoplasms
Carcinoid
Neuroendocrine carcinoma
others

Hematopoietic and lymphoid neoplasms
Lymphoma
others

Germ cell neoplasms

Metastatic neoplasms

Figure 1.3
The WHO classification of tumors of the kidney, 2004 (modified).

tumor-like lesions occurring in the kidney or in the perinephric fat. We divided the renal neoplasms into two groups named frequent tumors and other tumors. In the last one both the rarest tumors of the WHO 2004 classification and entities reported after the publication of this classification system have been included.

Gross and microscopic features

Handling of renal tumor specimens

The correct handling of the renal tumorectomy (Figure 1.4) or partial and radical nephrectomy by urologists and pathologists is essential in order to retrieve all the information useful for diagnosis and prognosis. The specimen should be brought immediately to the laboratory, fresh and without any cut from the operating room, to avoid any artifact which can cause inadequate sampling of the specimen, in particular regarding the evaluation of the surgical margins and the possible neoplastic infiltration of the perinephric fat. If for surgical reasons it is necessary to separate the perinephric adipose tissue, it must be sent indicating the zone of tumoral contact. The surgical margin in the nephron-sparing surgery specimens and the surface of the whole specimen, particularly the areas where the radicality is dubious, should be inked by the pathologist (Figure 1.4). After inspection of the renal vein, the pathologist should dissect the specimen obtained by a radical nephrectomy with a bivalving incision which should pass through the midline of the kidney in the coronal plane, photograph the bivalved kidney, take fresh neoplastic and normal tissues, and measure the diameter of the tumor. Afterwards some pathologists remove the perirenal fat (Gerota's fascia) with blunt dissection from the capsule and, if parts of the capsule are adherent to the tumor, dissect around them, leaving them in place so that they can be taken for histologic examination. Others leave the perirenal fat in place, directly make a series of parallel slabs in the sagittal plane at 2–3 cm intervals, and place the entire specimen in a container of buffered formalin for fixation overnight. The next step is the gross description of the tumor, which must include side, size, shape (ball-shaped, polygonal, uni- or multinodular, uni- or multifocal), border (sharpness of margins, pseudocapsule), color (yellow, gray-white, brown, tan-brown, beige), structural features, signs of regression (necrosis, hemorrhage, scars, pseudocysts), and extension (restricted to the kidney, infiltration of the perirenal adipose tissue or the hilar region (renal sinus), macroscopic invasion of hilar veins or pelvis, presence of lymph nodes and/or adrenal gland).

For histologic study the tissue samples have to be selected and separately identified from each centimeter of the largest diameter of the tumor, in particular from areas that differ in color, especially
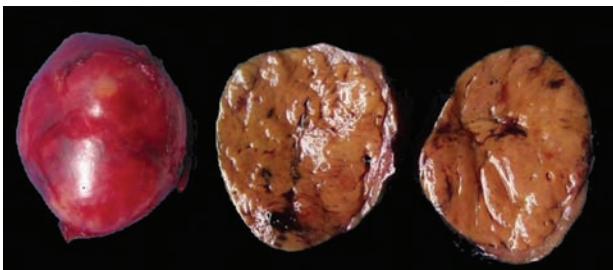
from areas which are white and gray, and from the periphery to document the interface with the normal renal parenchyma. The renal sinus is the fatty compartment located within the confines of the kidney not delineated from the renal cortex by a fibrous capsule. Because it contains numerous veins and lymphatics, invasion into this compartment may permit dissemination of a tumor otherwise regarded as renal-limited; more sections including the interface between the tumor and renal sinus have to be included. Again, additional sections should include the renal pelvis, renal artery and vein, ureter, lymph nodes, adrenal, and normal kidney (Figure 1.5).

Frequent tumors

Clear cell renal cell carcinoma

Clear cell renal cell carcinoma comprises 70% of all renal cell neoplasms and its male:female ratio is 2:1.

Grossly, it usually presents as a solitary, well-circumscribed (Figure 1.6) or multinodular, yellowish mass with additional gray and white foci; a pseudocapsule can sometimes be clearly evident (Figure 1.7). The yellow part corresponds to well-differentiated tumor areas, whereas the latter ones are less well differentiated. They are usually solid, but a few cases display a cystic growth pattern. White sclerotic septa (Figure 1.8), focal calcifications, necrosis, and irregular hemorrhage can be seen.[21] Under the light microscope, clear cell renal cell carcinoma shows solid, alveolar, and acinar patterns, the most common. The alveolar and acinar structures can be dilated and filled with red blood cells. Clear cell renal cell carcinoma contains a prominent, fine, delicate network of small thin-walled blood vessels (Figure 1.9). The clearing cytoplasm of the neoplastic cells is the result of an intensive accumulation of glycogen and lipids, which are dissolved in routine histologic processing. Many tumors contain neoplastic cells with eosinophilic cytoplasm due to increased numbers of mitochondria; this is particularly common in high grade
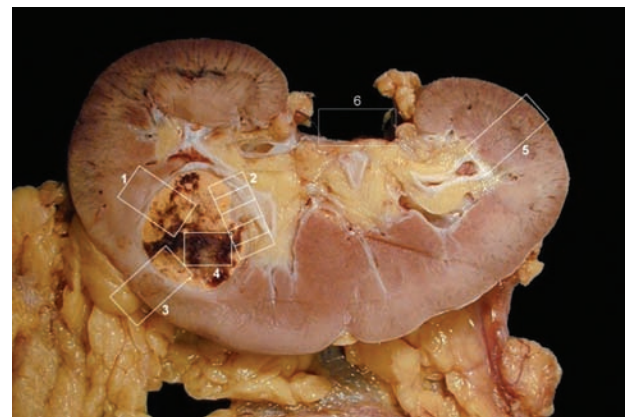
Figure 1.5
Sampling of renal tumor specimens. 1: Tumor and adjacent normal renal parenchyma; 2: tumor and adjacent renal sinus (multiple sections); 3: tumor and adjacent perirenal fat; 4: section per each particular area that differs in color (hemorrage, necrosis or scar); 5: normal cortical and medullary renal parenchyma; 6: section of the hilar region including ureter, branches of small arteries, veins and adipose tissue of the sinus. This section was taken before bevalving the specimen.

Figure 1.4
Renal tumorectomy: well-demarcated small brown nodule.
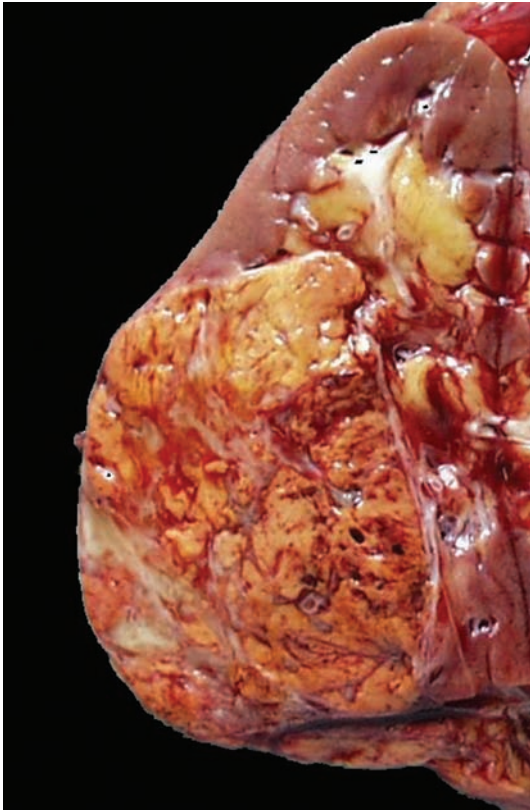
Figure 1.6
Clear cell renal cell carcinoma: a well-circumscibed, solitary, and yellowish large tumor.

Figure 1.8
Clear cell renal cell carcinoma: tumor with large sclerotic areas.
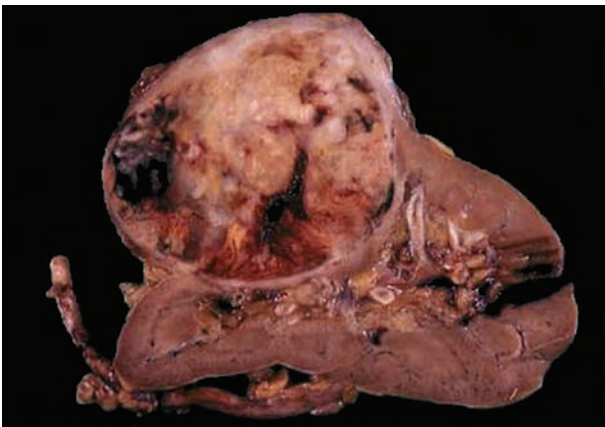
Figure 1.7
Clear cell renal cell carcinoma: tumor with a thick pseudocapsule and a variegation of color from yellowish to thin whitish areas and focal hemorrhage.
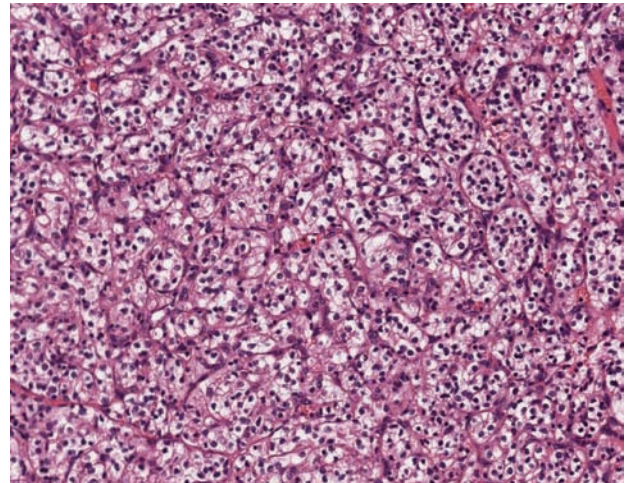
Figure 1.9
Clear cell renal cell carcinoma: a neoplasm with a solid-acinar pattern with a prominent, fine, delicate network of small thin-walled blood vessels.

tumors and in neoplastic cells adjacent to necrotic or hemorrhagic areas. Sarcomatoid change occurs in 5% of clear cell renal cell carcinomas and is associated with a poorer prognosis. Stage, nuclear grade, and necrosis are the most important prognostic features of this tumor.[17,21]

Rarely, the clear cell renal cell carcinoma presents as a mass entirely composed of cysts (Figure 1.10) lined for the most part by a single layer of clear epithelial cells and septa with no expansile solid nodules but containing aggregates of epithelial cells with clear cytoplasm, so called multilocular cystic renal cell carcinoma. These tumors are usually of low nuclear grade, confined to the kidney, and associated with an excellent prognosis. Approximately 40 cases have been described exclusively in adults, showing a predominance of males over females (3:1). Immunohistochemistry can be helpful in confirming the epithelial nature of the cells within the septa and lining the cysts.[22,23]
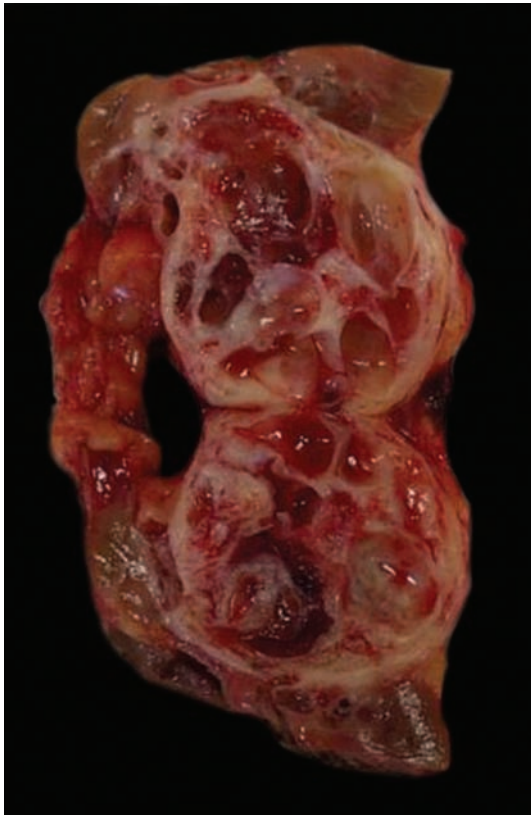
Figure 1.10
Multicystic clear cell renal cell carcinoma: mass entirely composed of cysts.

Figure 1.11
Papillary renal cell adenoma: small cortical tubulo-papillary neoplasm with a diameter less than or equal to 5 mm.

Figure 1.12
Papillary renal cell carcinoma exhibiting a central hemorrhage.

Papillary renal cell neoplasms

Papillary renal cell neoplasms are grossly characterized by a spherical boundary and a beige to white color. Tumors with a diameter up to 5 mm are considered adenomas (Figure 1.11). They are often incidental findings and occur in up to 23% of autopsy patients. The larger tumors are viewed as carcinomas, comprise 15% of all of surgically removed renal cell neoplasms, and the male to female ratio is 2:1. They can exhibit central necrosis resulting from a poor vascular supply and frequent hemorrhages (Figure 1.12). In some cases this feature can be so extensive as to mimic a cyst both radiologically and grossly.

Microscopically, papillary renal cell neoplasms are characterized by papillary or tubulo-papillary architecture.[24] The epithelial neoplastic cells line a delicate fibrovascular core in which aggregates of foamy macrophages can be found. The core can be expanded by edema. In carcinomas cholesterol crystals, necrosis, and hemorrhage are frequently seen and hemosiderin granules may be present in macrophages, stroma, and tumor cell cytoplasm.

Two well-recognized morphologic types of papillary renal cell carcinomas have been described. *Type 1* tumors have papillae covered by small cells with scanty cytoplasm, arranged in a single layer on the papillary basement membrane with low nuclear grade (Figure 1.13); *type 2* tumors are composed of cells with higher nuclear grade, eosinophilic cytoplasm, and pseudostratified nuclei on papillary cores (Figure 1.14). Type 1 tumors are more frequently multifocal. Psammoma bodies are common.[19,25,26] Longer survival

has been described for type 1 papillary renal cell carcinoma when compared with type 2.[27,28] A papillary renal cell carcinoma entirely composed of oncocytes has been described.[29] This subset of papillary tumors shows clinico-pathologic features different from type 1 and type 2 papillary renal cell carcinomas and has been proposed to be a third group, being intermediate between type 1 and type 2.

Sarcomatoid dedifferentiation is seen in approximately 5% of papillary renal cell carcinomas and has been associated with both type 1 and type 2 tumors.[30,31]

Chromophobe renal cell carcinoma

Chromophobe renal cell carcinoma accounts for 5% of all cases of surgically removed renal epithelial tumors, without any difference between males and females.[32]
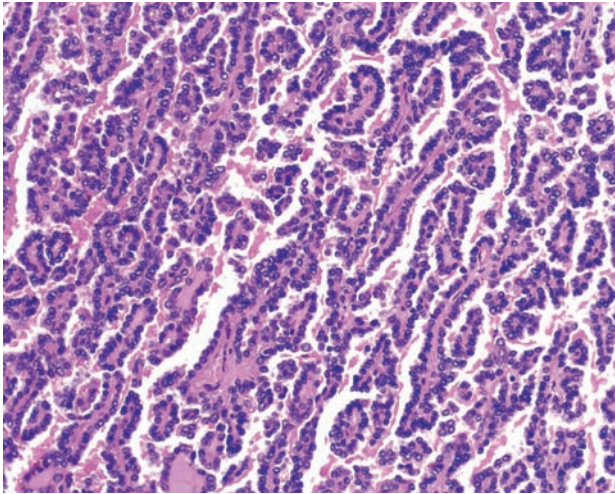
Figure 1.13
Papillary renal cell carcinoma: type 1 tumors have papillae covered by small cells with scanty cytoplasm, arranged in a single layer on the papillary basement membrane, and low nuclear grade.
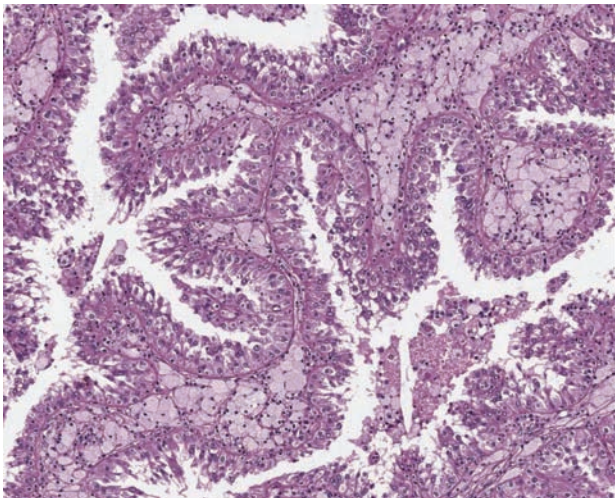
Figure 1.14
Papillary renal cell carcinoma: type 2 tumors are composed of cells with higher nuclear grade, eosinophilic cytoplasm, and pseudostratified nuclei on papillary cores.

Figure 1.15
Chromophobe renal cell carcinoma: solid well-circumscribed mass with a light brown color on the cut surface.
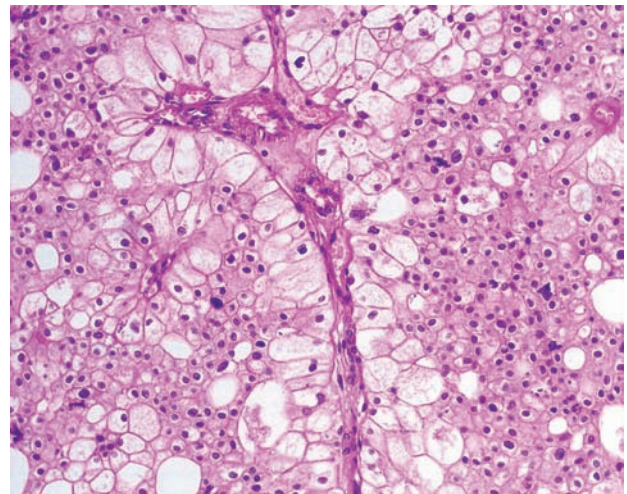
Figure 1.16
Chromophobe renal cell carcinoma: microscopically shows a solid, 'cobblestone' growth pattern whereas the acinar architecture surrounded by a rich vascular network as seen in clear cell renal cell carcinoma is lacking. The cytoplasm of a typical chromophobe is pale pink and flocculent and the peripheral portion of the cytoplasm shows a variable degree of granularity and eosinophilia, resulting in an accentuation of the cellular membrane. A perinuclear 'halo' may be observed. Nuclei range from vesicular to wrinkled and can exhibit pleomorphism. The neoplastic cells can display binucleation.

Grossly, it is a solid, well-circumscribed neoplasm with a light brown color on the cut surface (Figure 1.15). The morphologic features of chromophobe renal cell carcinoma include a solid, 'cobblestone' growth pattern, whereas the acinar architecture surrounded by a rich vascular network as seen in clear cell renal cell carcinoma is lacking. A tubular architecture may be occasionally seen.[33] Focal calcifications and broad fibrotic septa are frequently present. The cytoplasm of a typical chromophobe is pale pink and flocculent and the peripheral portion of the cytoplasm shows a variable degree of granularity and eosinophilia, resulting in an accentuation of the cellular membrane. A perinuclear 'halo' may be observed (Figure 1.16). Nuclei range from vesicular to wrinkled and can exhibit marked pleomorphism. The neoplastic cells can display binucleation. Mitotic figures can be found in a variable amount ranging from none to twenty-five × 50 high power fields.[34–39]

At electron microscopy chromophobe renal cell carcinoma is typically characterized by a cytoplasm containing scant numbers
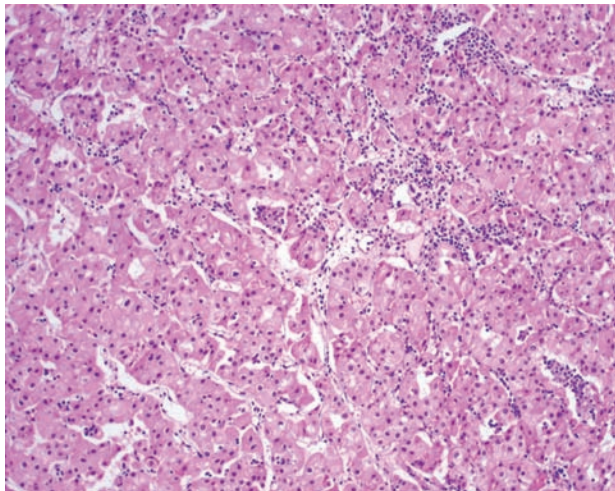
Figure 1.17
Chromophobe renal cell carcinoma: eosinophilic variant showing neoplastic cells with prevalent degree of granularity and eosinophilia.

Figure 1.18
Collecting duct carcinoma (so-called Bellini duct carcinoma): large gray-whitish bulging tumor arising from the medulla.

of mitochondria, which have tubulo-vesicular cristae, and by the presence of innumerable 150–300 micron microvesicles scattered between the mitochondria.[33,40,41] These microvesicles are responsible for the perinuclear halo and flocculent cytoplasm in the chromophobic neoplastic cells and can be used as a diagnostic finding.[41]

In 1988, 10 cases of eosinophilic variant out of 32 chromophobe renal cell carcinomas were identified.[34,42] This morphologic variant represents roughly 10% of this histotype (Figure 1.17). Chromophobe renal cell carcinoma is a low-grade malignancy; however, sarcomatoid transformation occurs in 8% of cases.

A diffuse cytoplasmic staining reaction with Hale's iron colloid stain has, for a long time, been considered a characteristic feature of this special tumor type only,[43] but it has recently been observed in acquired cystic disease-associated renal cell carcinomas.[44]

Collecting duct carcinoma (so-called Bellini duct carcinoma)

The group of tumors with collecting duct differentiation is undergoing considerable change and redefinition. The recommendation is to restrict the term 'collecting duct carcinoma' to the whitish and firm tumors grossly located in the medulla or central parts of the kidney. They are usually large and infiltrative with extension into the perinephric fat and invasion of the renal pelvis (Figure 1.18). Histologically, they are high-grade and highly aggressive carcinomas with papillary ductal architecture, stromal desmoplasia, and granulocytic infiltration (Figure 1.19). Lymph node metastases are common.[45] Some of them are associated with sickle cell trait and are grouped separately under the term medullary carcinoma.[46–48]

Oncocytoma

Renal oncocytomas are benign neoplasms. They comprise 5% of adult renal epithelial tumors in surgical series and the male to female ratio is 2:1.
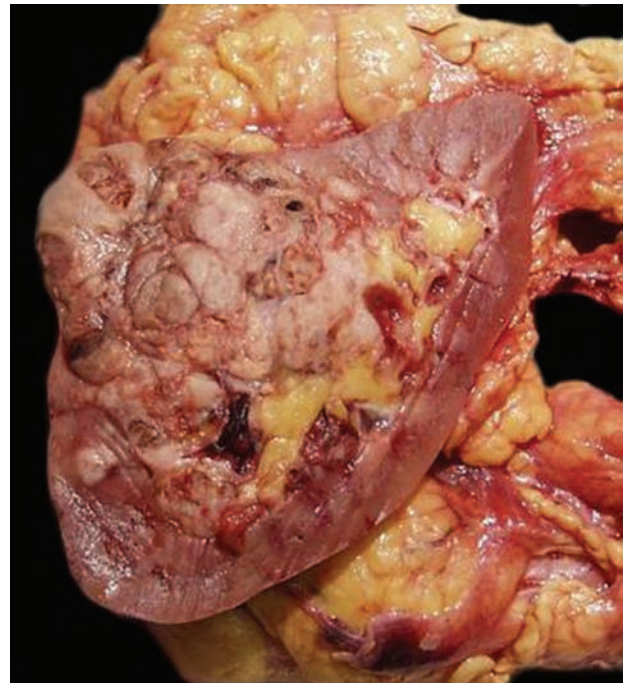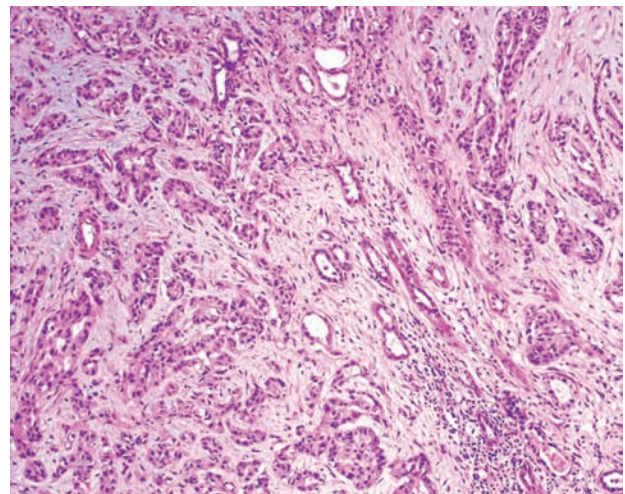
Figure 1.19
Collecting duct carcinoma: microscopically, it shows highly irregular duct-like structures, nests, and cords of cells in an abundant desmoplastic stroma.

The oncocytoma is a well-circumscribed large tumor with a stellate central scar and is a uniform mahogany brown color (Figure 1.20). Foci of hemorrhage can be observed, but necrosis is consistently absent.

Microscopically, oncocytoma displays a compact solid or nesting arrangement of large cells in an edematous and hyalinized stroma. Neoplastic cells have abundant granular eosinophilic cytoplasm,[49] reflecting the presence of the numerous mitochondria visible on
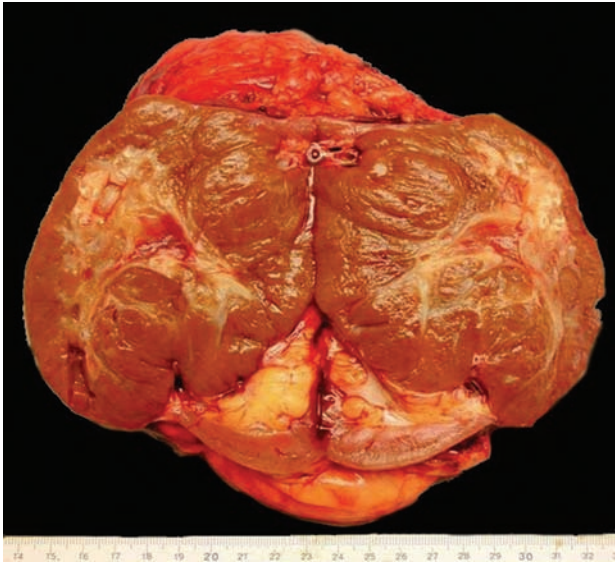
Figure 1.20
Renal oncocytoma: well-demarcated solid nodule with a tan color appearance and a stellate central scar.
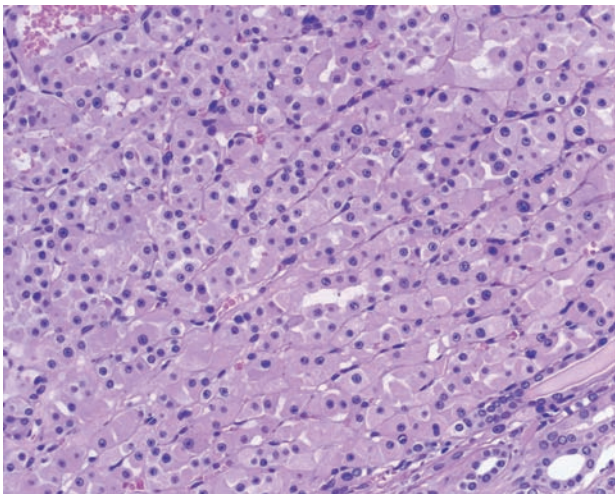
Figure 1.21
Renal oncocytoma: this tumor displays a compact solid or nesting arrangement of large cells with abundant granular cytoplasm; the nuclei of neoplastic cells are regular and round, with a nucleolus often evident.

ultrastructural analysis. The nuclei of renal oncocytoma cells are regular and round, with a nucleolus often evident (Figure 1.21). Rarely, occasional degenerative bizarre nuclei or scattered nests of small cells, so called oncoblasts, can be found. A tubulo-cystic pattern of growth can be prevalent in a few cases (Figure 1.22). The extension of oncocytoma cells into perirenal adipose tissue can occur in rare cases.[50–52]

The iron colloidal staining in renal oncocytoma is weak, distributed in focal areas, and in the form of fine, dust-like granules;[43] some authors have reported an apical positivity with Hale's colloidal iron staining in a group of renal oncocytomas.[53,54]
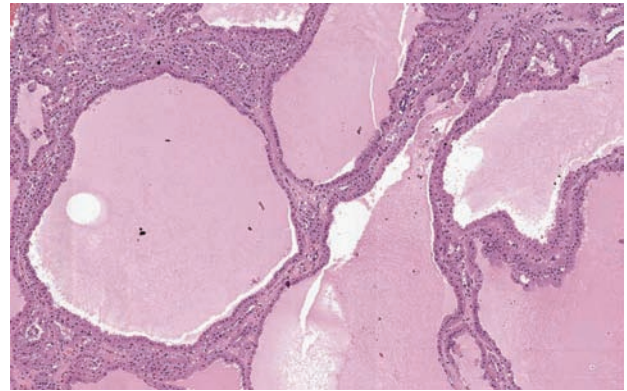
Figure 1.22
Renal oncocytoma: a tubulo-cystic pattern of growth can be observed in a few cases.

Metanephric adenoma

The family of metanephric neoplasms comprises a spectrum of lesions that are derived from the metanephric blastema such as metanephric adenoma, metanephric adenofibroma, and the metanephric stromal tumor.

Metanephric adenoma is the most frequently occurring member of this family. It is a benign tumor which occurs most commonly in women during their fifth decade of life. Approximately 10% of patients with this neoplasm present with polycythemia due to increased erythropoietin production.

Grossly, this tumor presents as a single, solid, well-circumscribed nodule with light brown to sandy cut surfaces of glassy quality (Figure 1.23). The tumors are sharply demarcated from adjacent parenchyma; hemorrhagic ones can be present. Necrosis and softening are not found, although cystic regression may occur in the center.

Histologically, metanephric adenoma consistently lacks a fibrous pseudocapsule. It is composed of densely packed, small, neoplastic cells with overlapping nuclei and invisible cell borders in solid-appearing areas, turning to a polar orientation in areas of more differentiated tubular, tubulo-papillary, or glomeruloid structures. The nuclei are innocent looking and mitoses are uncommon (Figure 1.24). It may contain psammoma bodies, especially in the peripheral sclerotic zones.[55–57]

Angiomyolipoma

Angiomyolipoma is the most common mesenchymal neoplasm of the kidney. It is classically composed of a variable mixture of fat, spindle and epithelioid smooth muscle cells, and abnormal thick-walled blood vessels. The perivascular epithelioid cell is considered to be the cell of origin for this and other related tumors[58] (Figure 1.25). Angiomyolipoma has, for a long time, been considered to be a hamartoma rather than a true tumor, but its clonal nature has been recently demonstrated. Angiomyolipoma can be sporadic or occurring in patients with tuberous sclerosis, an inherited syndrome. In patients with tuberous sclerosis, renal angiomyolipomas are found in both sexes, in the third and fourth decades of life; they are usually asymptomatic, bilateral, small, and multifocal (Figure 1.26).[59] Sporadic angiomyolipomas occur in older patients, in the fourth to sixth decades of life, with a female predominance; they are single,
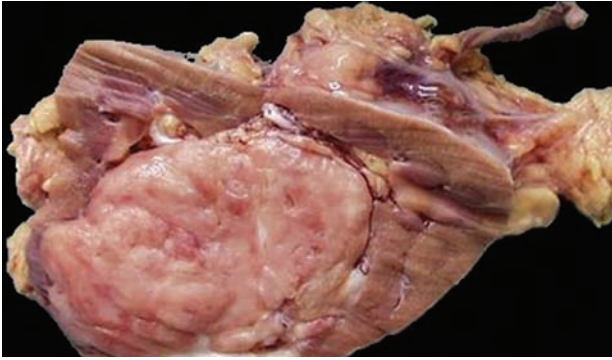
Figure 1.23
Metanephric adenoma: tumor well circumscribed but not encapsulated.
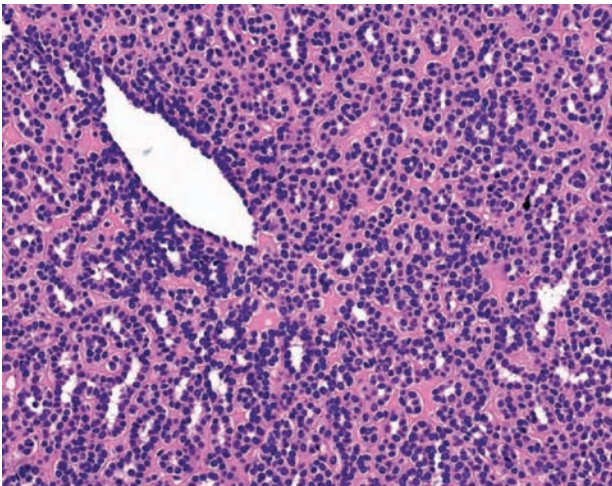
Figure 1.24
Metanephric adenoma: it is composed of densely packed small neoplastic cells with overlapping nuclei and invisible cell borders.
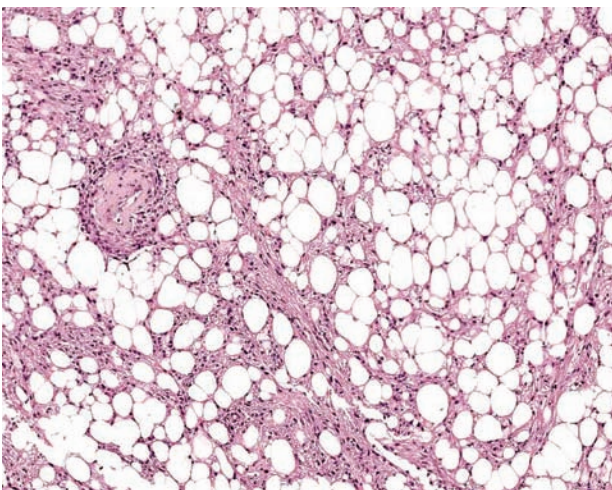
Figure 1.25
Renal angiomyolipoma: it is classically composed of a variable mixture of fat, spindle and epithelioid smooth muscle cells, and abnormal thick-walled blood vessels.

Figure 1.26
Renal angiomyolipoma: multiple renal tumors with variable maximum size.

unilateral, and larger than those associated with tuberous sclerosis. Classic angiomyolipoma contains more than one cell type, but occasionally adipocytes (lipoma-like angiomyolipoma) or spindle smooth muscle cells (leiomyoma-like angiomyolipoma) predominate in particular lesions.

Classic angiomyolipoma has a benign outcome. Multifocality and regional lymph node involvement can occur and this is considered to represent a multifocal growth pattern rather than metastasis.[60] Three cases of sarcoma developing in sporadic angiomyolipoma have been reported.[61]

Angiomyolipoma frequently shows loss of heterozygosity of variable portions of the *TSC2* gene locus in both sporadic and tuberous sclerosis-associated tumors, but loss of heterozygosity of the *TSC1* gene is only occasionally found.[62]

Microscopic angiomyolipomas (so-called microhamartomas) are small nodules often present in the renal parenchyma bearing angiomyolipomas. They are dishomogeneous in appearance and display all the varied histologic features of angiomyolipoma less the thick-walled blood vessels.[63]

Intraglomerular lesions with features overlapping with those of angiomyolipoma have been reported in patients with and without tuberous sclerosis and in the *TSC2/PKD1* contiguous gene syndrome, a disease with a deletion disrupting both TSC2 and PKD1 (autosomal dominant polycystic disease gene).[64]

Epithelioid angiomyolipoma is now a well-recognized variant of angiomyolipoma.[65–67] This tumor is composed of purely epithelioid cells (Figure 1.27) with melanogenesis markers immunoreactivity, such as HMB45 and melan-A arranged in sheets and characterized by the absence of both adipocytes and abnormal blood vessels. The neoplastic cells display a cytoplasm varying from faintly eosinophilic to clear, and with considerable nuclear atypia. Epithelioid angiomyolipoma closely resembles high-grade or sarcomatoid renal cell carcinomas and it is responsible for the occasionally misdiagnosed angiomyolipoma. It can recur locally, metastasize, and cause death. At the present time, on the basis of histology alone, it is not possible to predict malignant behavior in these neoplasms and all epithelioid angiomyolipomas should be closely followed clinically. Epithelioid angiomyolipoma has been described in patients with and without
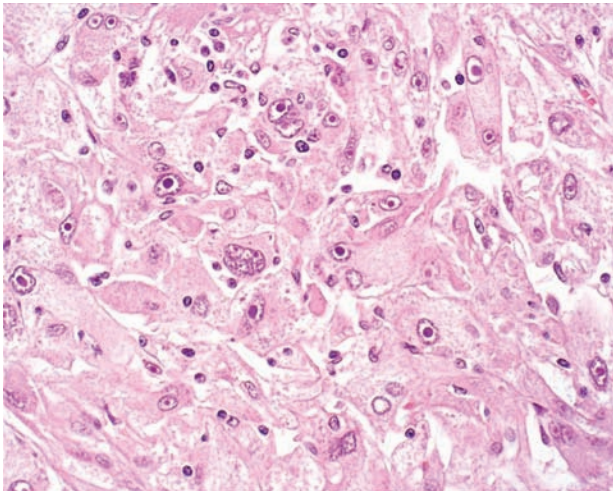
Figure 1.27
Epithelioid renal angiomyolipoma: epithelioid neoplastic cells with considerable nuclear atypia.
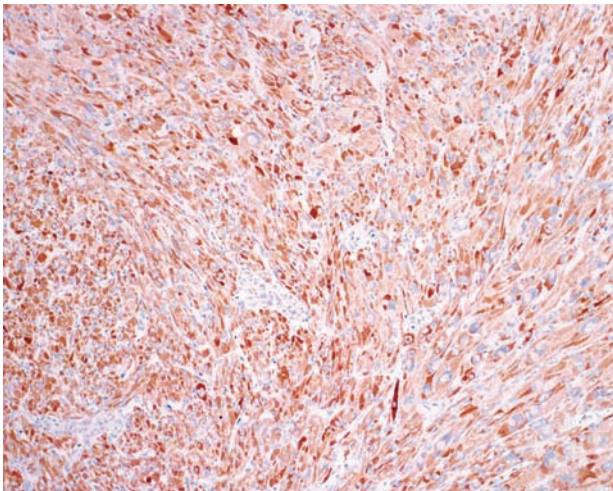
Figure 1.28
Epithelioid renal angiomyolipoma: HMB45 diffuse positive immunoexpression in both epithelioid and spindle cells.

evidence of tuberous sclerosis,[66,67] and in the *TSC2/PKD1* contiguous gene syndrome.[64] Loss of heterozygosity of TSC2 has been reported in two cases of sporadic epithelioid angiomyolipoma.[66,68]

Neoplasms composed of a population of HMB45 positive polygonal cells (Figure 1.28) with deeply eosinophilic cytoplasm have been identified in patients with and without tuberous sclerosis and called oncocytoma-like angiomyolipoma.[69]

Cystic angiomyolipoma (or angiomyolipoma with epithelial cysts) is a recently described variant of angiomyolipoma.[70] At gross examination, it has a composite aspect: solid and cystic. Microscopically, it shows three components:

1. epithelial cysts lined by cuboidal to hobnail cells, positive for cytokeratin;
2. a compact subepithelial 'cambium-like' layer of stromal cells positive for HMB45, melan-A, estrogen receptors, progesterone receptors, and CD10; and

3. a solid extracystic component with the morphology of a muscle-predominant angiomyolipoma.

Only 1 of the 15 cases described to date had a known history of tuberous sclerosis.[70,71]

Rare tumors

Renal carcinomas associated with Xp11.2 translocations

Most renal carcinomas with Xp11 translocations have occurred in children and young adults; occasional adult cases have also been reported. Xp11.2-associated carcinomas likely comprise approximately one-third of pediatric renal cell carcinomas. Several Xp11 translocation carcinomas have arisen in patients previously exposed to chemotherapy.

Grossly, they display features similar to clear cell renal cell carcinoma. Histologically, a papillary carcinoma composed of clear cells with a variable number of psammoma bodies is the most distinctive histopathologic appearance of an Xp11 translocation carcinoma (Figure 1.29), however the morphologic features of Xp11-translocation carcinomas associated with specific chromosome translocation breakpoints differ (Figure 1.30). The most distinctive immunohistochemical feature of all these neoplasms is nuclear labeling for TFE3 protein using an antibody to the C-terminal
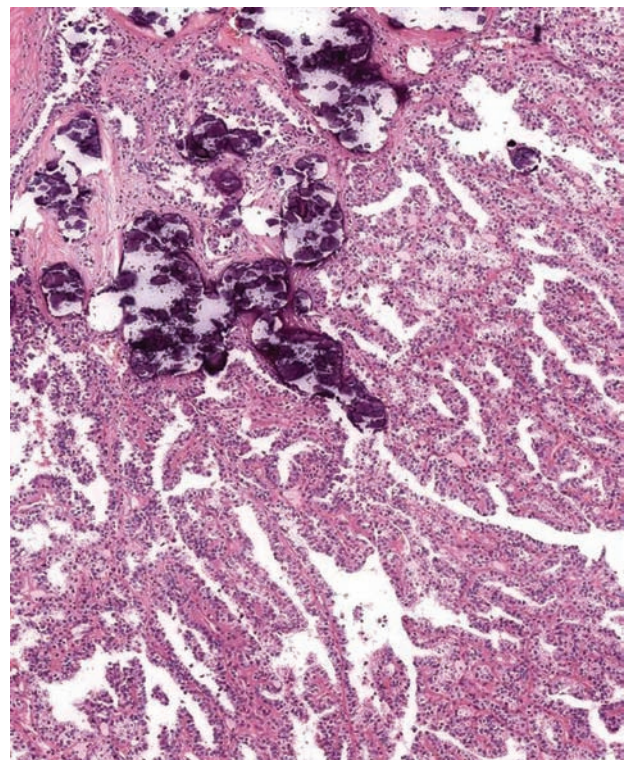
Figure 1.29
Renal cell carcinoma with Xp11 translocation: a papillary carcinoma composed of clear cells with a variable number of psammoma bodies is its most distinctive histopathologic appearance.
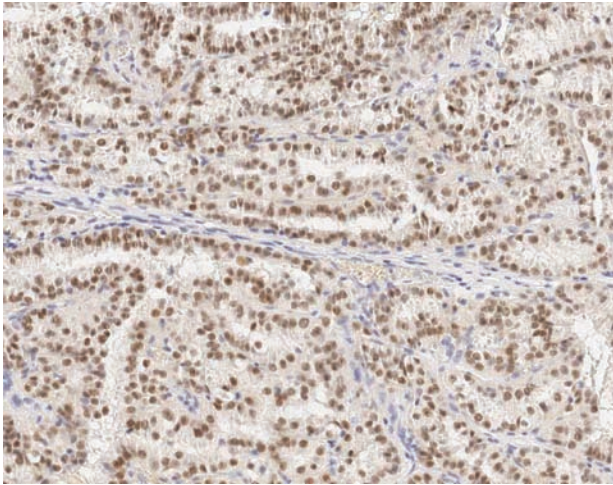
Figure 1.30
Renal cell carcinoma with translocation: TFE3-positive nuclear immunoexpression.

Figure 1.31
Renal cell neoplasm with t(6;11) translocation: this tumor is composed of nests and tubules of polygonal epithelioid cells with clear to granular eosinophilic cytoplasm and round nuclei with small nucleoli. A second population of smaller epithelioid cells is also characteristic, typically clustered around nodules of hyaline basement membrane material.

portion of TFE3, which is retained in the gene fusions.[72–75] Their clinical behavior remains to be determined.

A group of renal tumors characterized by another translocation, t(6;11)(p21;q12), has been recently identified. These neoplasms are composed of nests and tubules of polygonal epithelioid cells with clear to granular eosinophilic cytoplasm and round nuclei with small nucleoli. A second population of smaller epithelioid cells is also characteristic, typically clustered around nodules of hyaline basement membrane material[76] (Figure 1.31). The cases examined have generally been negative for cytokeratins by immunohistochemistry, but all have labeled at least focally for the melanogenesis markers, HMB45 and melan A. Recently, the immunohistochemical expression of TFEB protein has been described and suggested as a useful tool for the diagnosis of this neoplasm (Figure 1.32).[77]

Renal cell carcinomas after neuroblastoma

These rare tumors typically affect children (median age 13.5 years) who are long-term survivors of neuroblastoma. They feature oncocytoid cytoplasm that is often voluminous, and have solid and papillary architecture. Several cases have arisen in children who never received chemotherapy for their neuroblastoma so it is possibly a genetic susceptibility.[78,79]

Mucinous tubular and spindle cell carcinoma

Mucinous tubular and spindle cell carcinoma has been reported with different terminology in the literature, such as low-grade myxoid renal epithelial neoplasm of distal nephron differentiation, low-grade tubular-mucinous renal neoplasm, and Henle loopoma. It arises during the sixth decade of life with a sharp prevalence for the female sex (male to female ratio is 1:4). Grossly, it is a solid, pale tan to yellow to gray-white lesion that may have slight focal areas of necrosis or hemorrhage. This tumor is circumscribed and
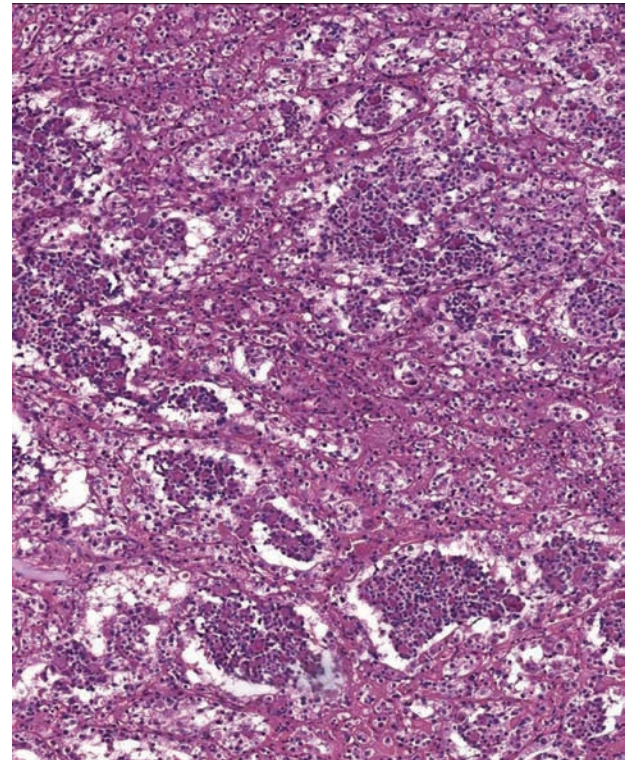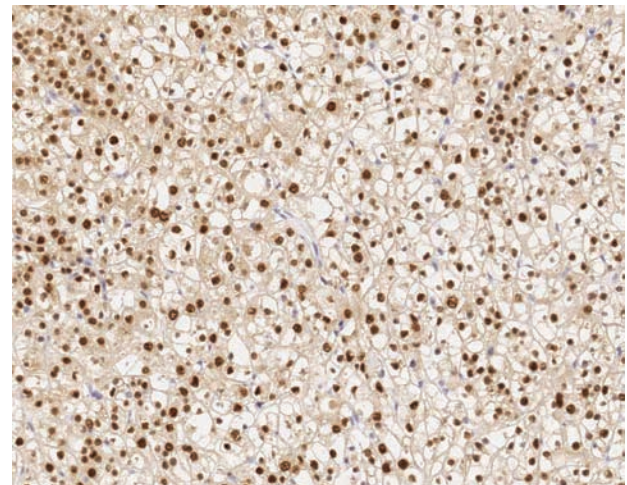
Figure 1.32
Renal cell neoplasm with t(6;11): TFEB-positive nuclear immunoexpression.

features branching, elongated tubules in a bubbly, basophilic, myxoid stroma (Figure 1.33). Tumor cells are predominantly cuboidal with scant, clear to pale, acidophilic cytoplasms and low-grade nuclear features.[78,80–82]
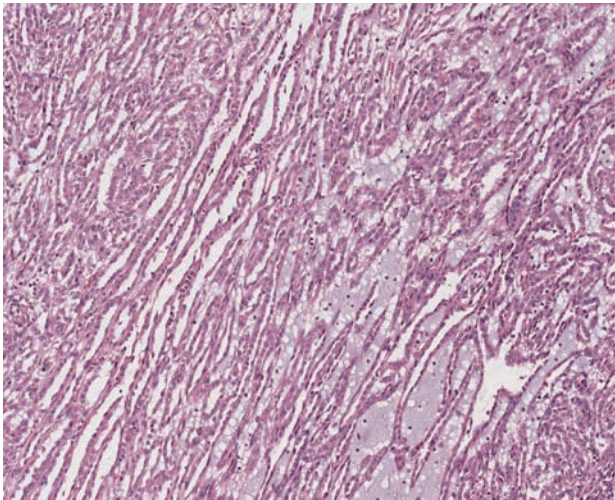
Figure 1.33
Mucinous tubular and spindle cell carcinoma: it shows branching, elongated tubules in a bubbly, basophilic, myxoid stroma. Tumor cells are predominantly cuboidal with scant, clear to pale, acidophilic cytoplasm and low grade nuclear features.

Only rare cases have metastasized to lymph nodes: most are cured by excision and no tumor-related deaths are on record.[83]

Renomedullary interstitial cell tumors and other mesenchymal tumors

Renomedullary interstitial cell tumors (medullary fibromas) are well-circumscribed, small (<1 cm), gray-white nodules in the renal medulla, often multiple, which are found in as many as 50% of autopsied kidneys. They are benign lesions composed of small spindle cells in a loose basophilic stroma (Figure 1.34). Other benign (juxtaglomerular cell tumor, leiomyoma, lipoma, hemangioma, lymphangioma) and malignant (leiomyosarcoma, liposarcoma, solitary fibrous tumor, hemangiopericytoma, fibrosarcoma, fibrous histiocytoma) mesenchymal neoplasms are extremely rare.

Cystic nephroma

Cystic nephromas are benign neoplasms occurring predominantly in women (female to male ratio is 8:1) and are often found incidentally by radiologic examinations for other conditions. They may present as a single, rarely bilateral mass with pain or hematuria. Grossly, cystic nephromas are well demarcated from adjacent normal kidney by a thick fibrous pseudocapsule and herniate into the renal sinus or bulge from the convexity of the renal cortex. The tumor is completely cystic and there are no solid nodules (Figure 1.35). The cysts contain clear or hemorrhagic fluid and range in size from microscopic to 5 cm or greater. The septal stroma consists of fibrous tissue which varies from myxoid to collagenous and occasionally it is cellular and has a wavy appearance resembling ovarian stroma. Necrosis and hemorrhage are rare. The cysts are lined by flattened, cuboidal, or hobnail epithelium, occasionally with a clear cytoplasm (Figure 1.36). Mitotic figures are very rare. Rarely sarcoma arising in cystic nephroma has been reported.[22,84]
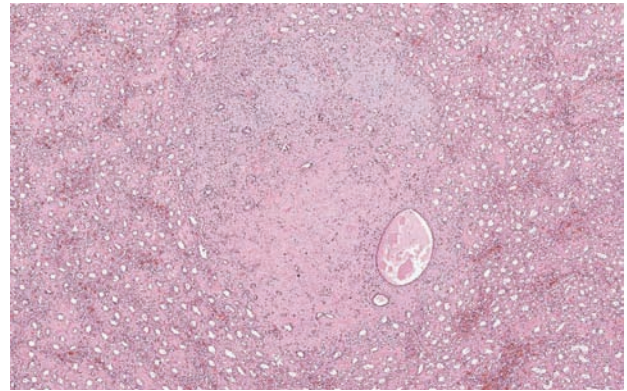
Figure 1.34
Renomedullary interstitial cell tumors: small medullary interstitial proliferation surrounded by normal parenchyma.
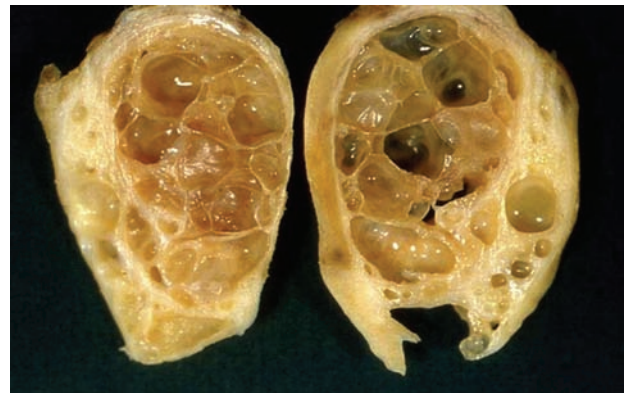
Figure 1.35
Cystic nephroma: encapsulated mass entirely composed of cysts ranging in size from a few millimeters to some centimeters.
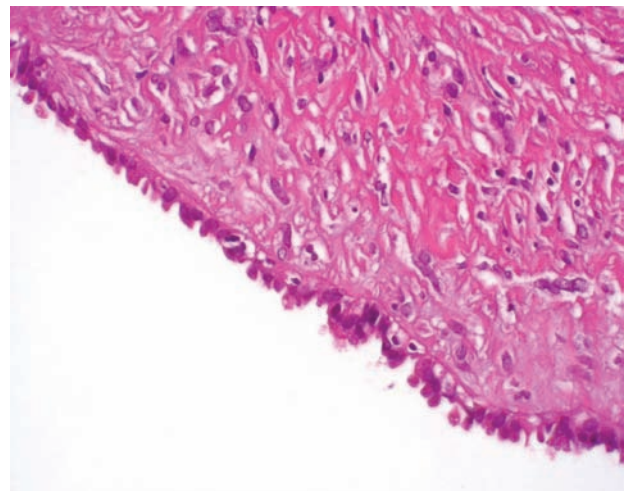
Figure 1.36
Cystic nephroma: the cysts are lined by a single layer of hobnail epithelium.

Mixed epithelial and stromal tumors

This tumor has been previously reported as cystic hamartoma of the renal pelvis and mesoblastic nephroma of adults. It shows a strong predominance in women during the perimenopausal period. Most of the tumors appear to arise in the middle kidney, often with herniation into the renal pelvic cavity, and to grow as a well-circumscribed, unencapsulated mass.

Grossly, it is composed of multiple cysts and solid areas (Figure 1.37). Histologically it displays a mixture of neoplastic epithelial components and spindle cells (Figure 1.38). The spindle cell proliferation resembles ovarian stroma and it is intermixed with cysts lined by flat, cuboidal, or hobnailed epithelial cells, typical of collecting-duct epithelium. Urothelium, which may be hyperplastic, may also line some of the cysts. Blood vessels with thick walls and fat cells may be present.[85,86]

Neuroendocrine renal tumors

Although neuroendocrine cells have not been documented in the normal renal parenchyma, a few neuroendocrine neoplasms arise in the kidney. These rare tumors include carcinoids and small cell neuroendocrine carcinomas, whereas pure intrarenal neuroblastoma and paraganglioma/pheochromocytoma are exceedingly rare findings.

Carcinoids are well-differentiated neuroendocrine tumors which seem to show a striking association with horseshoe kidney. They occur in patients over 40 years of age as solitary, solid, well-circumscribed yellowish nodules. About 30% of these tumors metastasize. Small cell neuroendocrine carcinomas are large, whitish, invasive masses arising in patients with an average age of 60 years and their prognosis is extremely poor. Both carcinoids and small cell neuroendocrine carcinomas do not differ morphologically from similar tumors located at other sites[87–89] (Figures 1.39 and 1.40).

Figure 1.37
Mixed epithelial and stromal tumors: the tumors are typically composed of multiple cysts and solid areas.
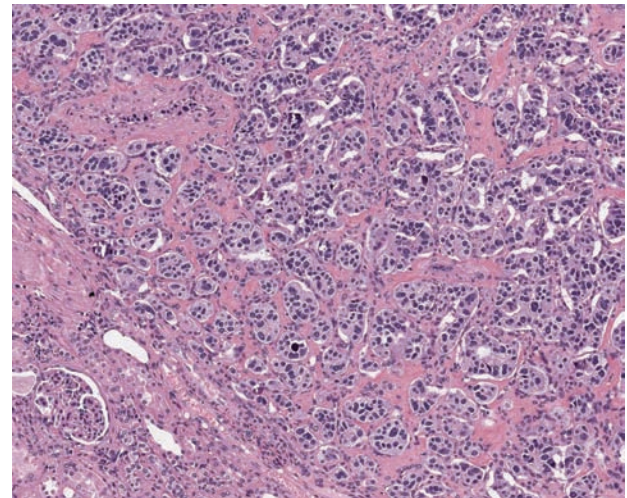
Figure 1.39
Carcinoid renal tumor: this does not differ morphologically from similar tumors located at other sites.

Figure 1.38
Mixed epithelial and stromal tumor: it is composed of large cysts and stroma comprising a variable cellular population of spindle cells.
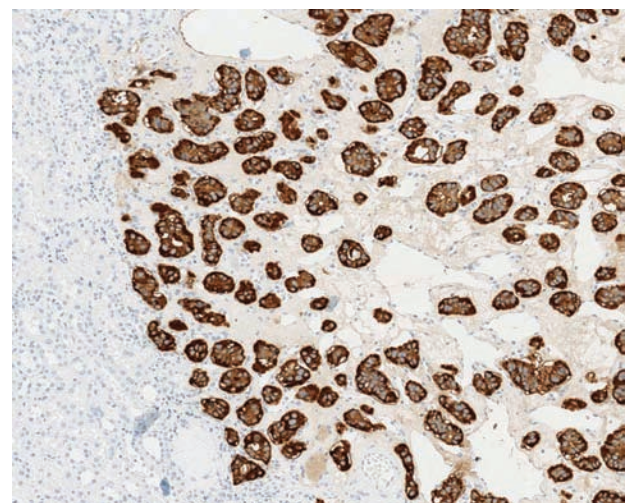
Figure 1.40
Carcinoid renal tumor: positive immunoexpression of chromogranin.

Lymphoproliferative diseases

Both primary and secondary lymphomas and involvement by plasmacytomas and leukemias can be observed in the kidney. The patterns of renal involvement can be either diffuse or with the formation of masses or intravascular[90] (Figures 1.41 and 1.42).

Metastatic tumors

In the advanced stages of evolution of malignant neoplasms at other locations, renal metastases can occur; however, infrequently they are the primary manifestation of the disease (Figures 1.43 and 1.44).

Figure 1.41
Primary renal lymphoma: diffuse pattern of neoplastic lymphoid renal involvement.

Figure 1.42
Primary renal lymphoma: CD20-positive immunoexpression of lymphoid neoplastic proliferation.

Figure 1.43
Follicular thyroid carcinoma metastatic to the kidney.

Figure 1.44
Renal metastasis of a carcinoma of the thyroid: TTF-1 immunoexpression in the metastatic thyroid tumor.
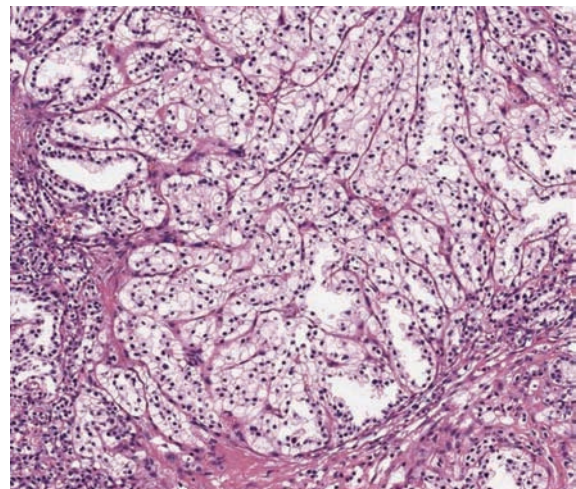
Figure 1.45
Renal cell neoplasm in end-stage renal disease: clear cell papillary renal cell carcinoma of the end-stage renal disease kidney is composed of clear cells with low grade nuclei arranged in a solid-acinar, tubular, microcystic, or papillary architecture.

Renal cell neoplasms in end-stage renal disease

End-stage renal disease is known to be associated with an increased risk of developing renal cell neoplasms, particularly in patients with acquired cystic disease secondary to long-term hemodialysis. Tumors arising in kidneys with end-stage renal disease include those resembling sporadic renal tumors, such as clear cell, papillary and chromophobe renal cell carcinomas, and tumors distinct from them named acquired cystic disease-associated renal cell carcinoma and clear cell papillary renal cell carcinoma of the end-stage renal kidneys (Figure 1.45).[50] The last two groups of neoplasms seem to display distinctive histologic features not easily referable to the histotypes described in the WHO 2004 classification system. The
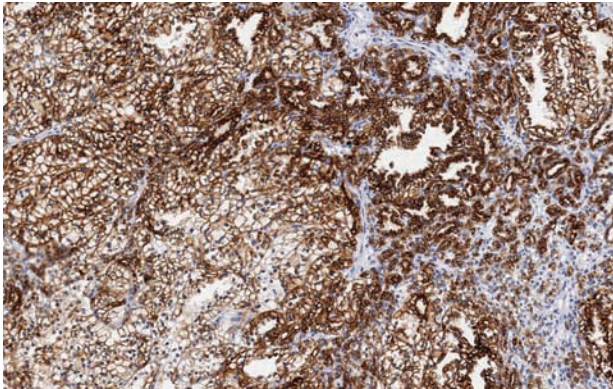
Figure 1.46
Renal cell neoplasm in end-stage renal disease: CK7-positive immunoexpression in clear cell papillary renal cell carcinoma.
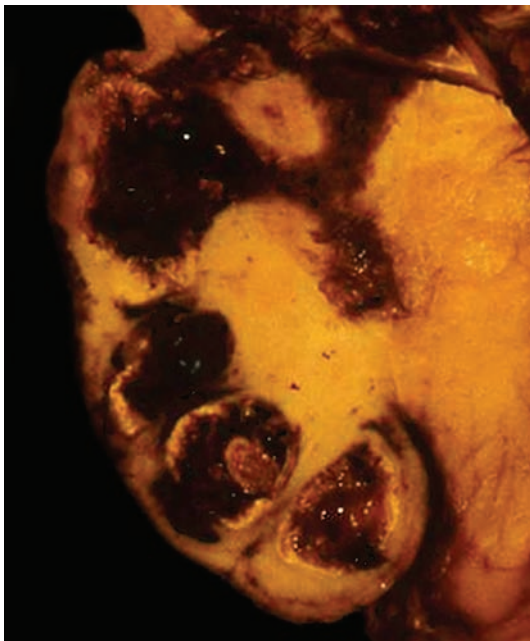
Figure 1.47
Xanthogranulomatous pyelonephritis is a tumor-forming subacute or chronic inflammation which can be associated with nephrolithiasis.
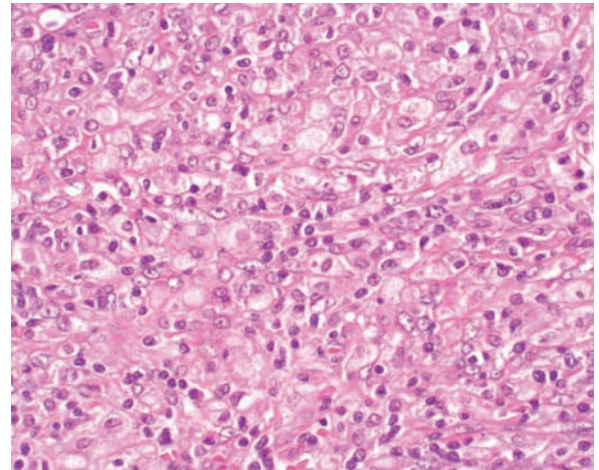
Figure 1.48
Xanthogranulomatous pyelonephritis is a tumor-forming subacute or chronic inflammation; it is composed of lipid-laden macrophages (xanthoma cells) which may mimic the neoplastic cells of clear cell renal cell carcinoma. Multinucleated giant cells, spindled fibroblasts, and inflammatory cells, in particular granulocytes, are frequently present.
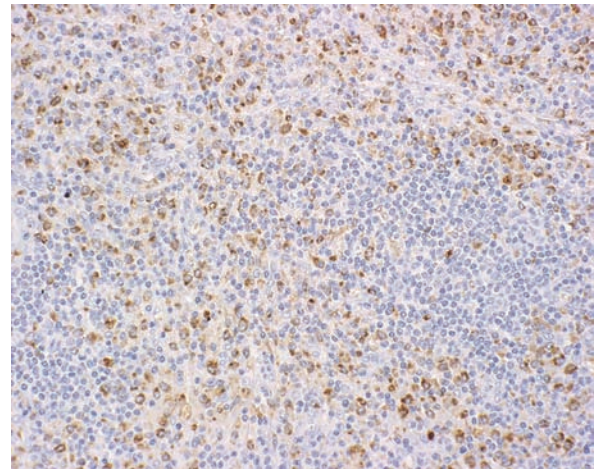
Figure 1.49
Xanthogranulomatous pyelonephritis: CD68-positive immunoexpression of macrophages (xanthoma cells).

acquired cystic disease-associated renal cell carcinoma is characterized by abundant eosinophilic cytoplasm, a variably solid, cribriform tubulo-cystic and papillary pattern, and by deposits of calcium oxalate crystals.

Clear cell papillary renal cell carcinomas of the end-stage renal kidneys are composed of clear cells with low grade nuclei arranged in a solid-acinar, tubular, microcystic, or macrocystic architecture with prevalently cytokeratin 7 immunoexpression (Figure 1.46). Occasional tumors like these have been observed in a non end-stage renal disease setting. A peculiar morphologic feature is the polarization of the nuclei in a linear array away from the basal aspects of the cells.
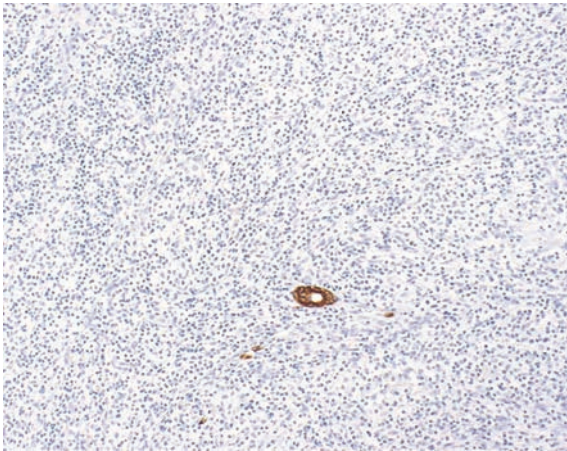
Figure 1.50
Xanthogranulomatous pyelonephritis: absence of cytokeratin 8-18 (CK8-18) immunoexpression of macrophages; entrapped normal renal tubules immunostain for CK8-18.
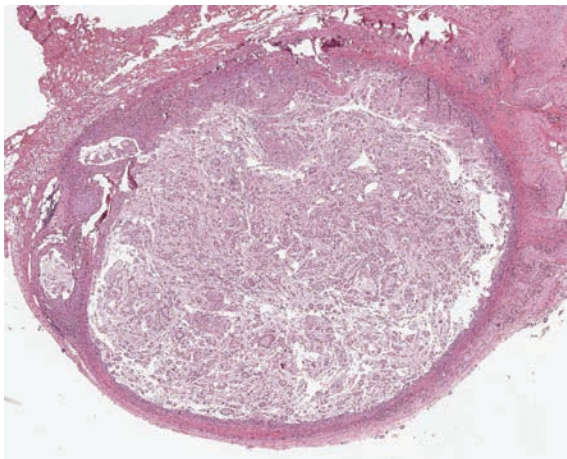
Figure 1.51
Hemorrhagic cyst: a perirenal cyst that can radiologically mimic a solid mass or a complicated cyst.
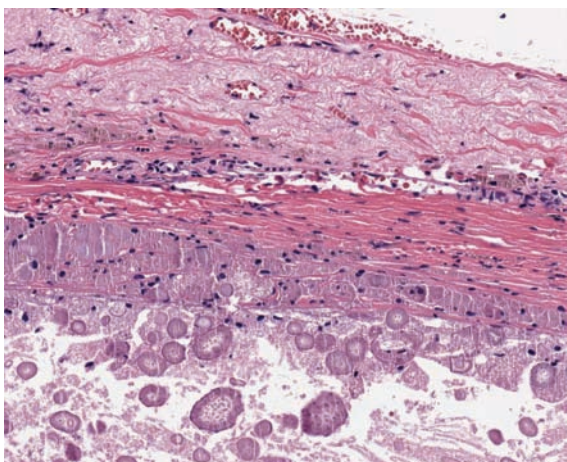
Figure 1.52
Hemorrhagic cyst: the morphologic hallmark of this cyst without identifiable epithelium is the presence of numerous round laminated bodies in the inflammatory wall, called Liesegang rings.
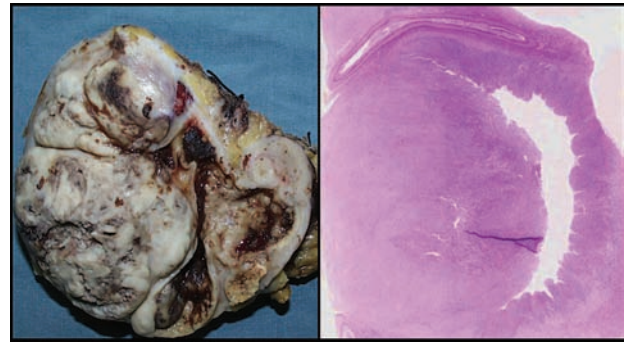
Figure 1.53
Malakoplakia: grossly it may present as a plaque or nodule (left); microscopically, a whole histologic section mimics renal cell carcinoma (right).
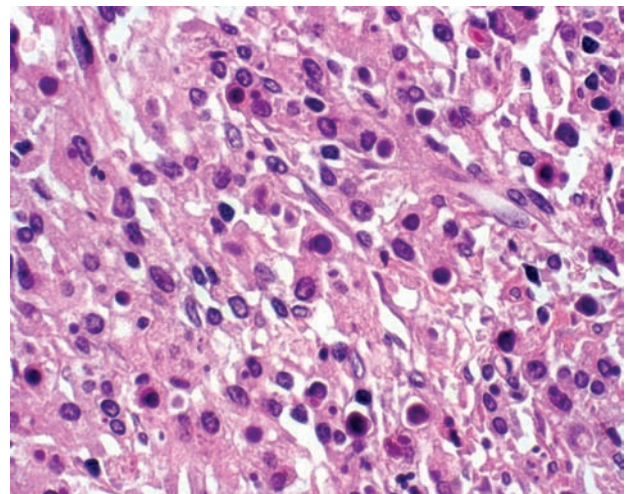
Figure 1.54
Malakoplakia: it can present as a renal solid mass which is composed of eosinophilic macrophages with intracytoplasmic Michaelis–Gutman bodies.
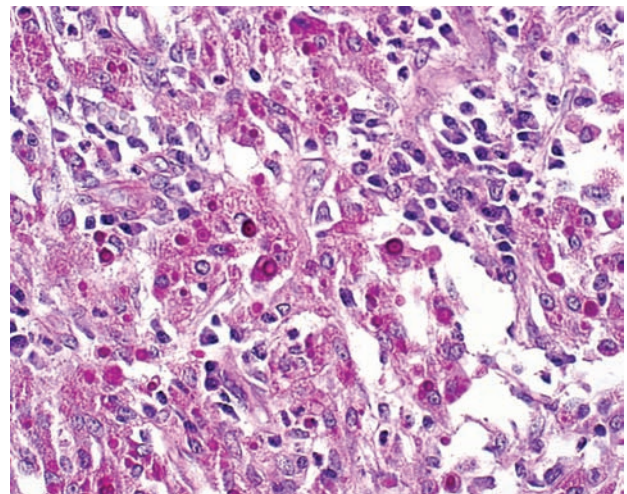
Figure 1.55
Malakoplakia: evidence of eosinophilic macrophages with intracytoplasmic Michaelis–Gutman PAS-positive bodies.
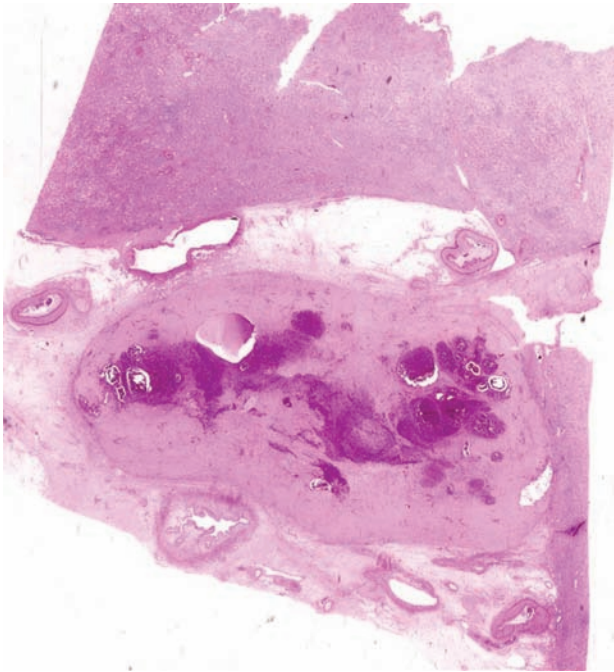
Figure 1.56
Pseudotumor due to Tamm–Horsfall extravasation: the extravasation of large amounts of this protein in the adipose tissue of the sinus simulates clinically and radiologically a tumor of the renal pelvis.

Tumor-like lesions

The lesions that most frequently simulate neoplasms clinically and radiologically are xanthogranulomatous pyelonephritis, perirenal and intrarenal hemorrhagic cysts, malakoplakia, and pseudotumor due to Tamm–Horsfall extravasation.

Xanthogranulomatous pyelonephritis is a tumor-forming subacute or chronic inflammation which can be associated with nephrolithiasis (Figure 1.47) to a variable degree, ranging from 20 to 70% of the cases. Grossly it appears as golden yellow nodules which are histologically composed of lipid-laden macrophages (xantoma cells) (Figure 1.48). However, these cells immunostain for CD68 (Figure 1.49), but not for cytokeratin 8-18 (Figure 1.50), and may mimic the neoplastic cells of clear cell renal cell carcinoma. Multinucleated giant cells and spindled fibroblast and inflammatory cells, in particular granulocytes, are frequently present.

Perirenal and intrarenal hemorrhagic cysts can radiologically mimic a solid mass or a complicated cyst (Figure 1.51). The morphologic hallmark of this cyst, frequently without identifiable epithelium, is the presence of numerous round laminated bodies called Liesegang rings in the inflammatory wall[91,92] (Figure 1.52).

Malakoplakia can present as a renal solid mass (Figure 1.53) which is composed of eosinophilic macrophages (Figure 1.54) with intracytoplasmic Michaelis–Gutman PAS-positive bodies (Figure 1.55).[93]

Tamm–Horsfall protein is a kidney-specific protein which is produced in the Henle's loop. The extravasation of large amounts of this protein in the interstitium or in the adipose tissue of the sinus can be clinically and radiologically misdiagnosed for a tumor (*pseudotumor due to Tamm–Horsfall extravasation*) (Figures 1.56 and 1.57).[94,95]

Figure 1.57
The immunostain of Tamm–Horsfall protein demonstrates the nature of the amorphous eosinophilic material present in the adipose tissue of the renal sinus.

Part 3

Tumor genetics

The genetic studies of renal tumor have resulted in improved understanding of the biologic mechanisms that are responsible for neoplastic development and progression. It has also been revealed that several different and specific genetic events are responsible for tumorigenesis in the various categories and subcategories of renal neoplasms. The ultimate goal of research on the molecular pathology of renal neoplasms is a complete understanding of the genetics of these tumors, which will, in turn, aid in making the correct diagnosis, accurately assessing prognosis, and selecting appropriate and targeted therapeutic options.
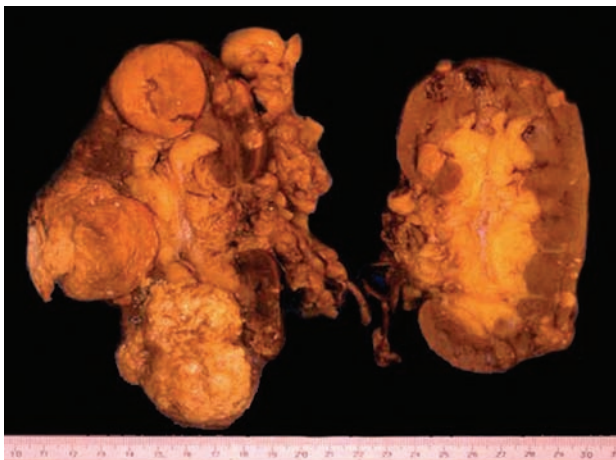
Figure 1.58
Multifocal papillary cell renal cell carcinoma: multiple parenchymal tumors.

Renal tumors occur predominantly as a sporadic disease, but also have familial forms. In the former, the kidney is affected by a solitary renal nodule; in the latter, the kidney/s are affected by multiple and bilateral neoplasms (Figure 1.58). Most genetic analyses show that both sporadic and familial tumors arise as the result of the same chromosomal abnormalities.

Clear cell renal cell carcinomas show a highly specific deletion of chromosome 3p (Figure 1.59), which is considered one of the primary events in the development of this tumor. Allelic losses of 3p have been mapped to three distinct chromosomal regions, 3p14 (FHIT gene), 3p21.3, and 3p.25, both in sporadic and hereditary forms of this cancer. Mutation of the Von Hippel–Lindau syndrome (VHL) gene (3p25) occurs exclusively in this type of renal tumor but it is not associated with tumor stage or grade.[96–100]

Von Hippel–Lindau disease is a rare, autosomal dominant, familial cancer syndrome consisting chiefly of retinal angiomas, hemangioblastomas of the central nervous system, pheochromocytomas, and clear cell renal cell carcinoma. In this disease, one *VHL* allele is inherited with a mutation. Associated focal lesions, such as renal cell carcinoma, arise from the inactivation or silencing of the remaining normal (wild-type) *VHL* allele (Figure 1.60).[101,102] Remarkably, defects in the *VHL* gene also appear to be responsible for about 60% of the cases of sporadic clear cell renal cell carcinoma.[102–104]

Papillary renal cell carcinoma is characterized by trisomy (Figures 1.61 and 1.62) of chromosomes 3q, 7, 8, 12, 16, 17, and 20 and loss of the Y chromosome; these most consistent genetic abnormalities are present in both solitary and multifocal papillary renal cell carcinomas and they occur early in the evolution of this neoplasm.[99,105–107] Some authors have suggested genetic differences between type 1 and type 2; type 1 papillary renal cell carcinoma cases seem to have a significantly higher frequency of allelic imbalance on 17q than type 2 cases, and type 2 cases a higher frequency of allelic
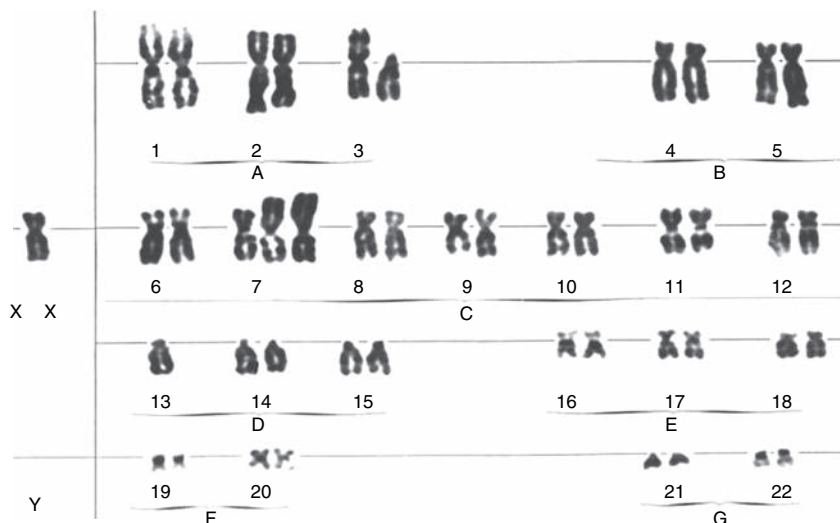
Figure 1.59
Clear cell renal cell carcinoma: karyotype showing loss of chromosome 3p.
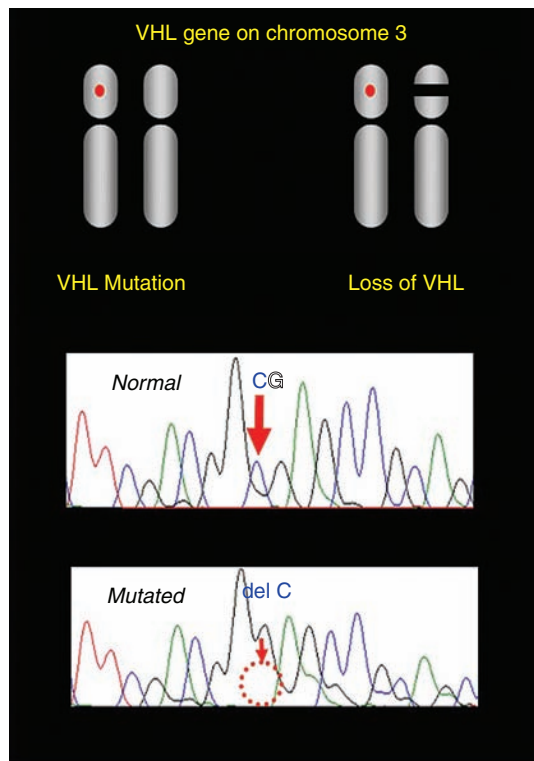
Figure 1.60

The upper part of the figure illustrates the general mechanism of VHL gene inactivation, consisting of the mutation of one allele and the loss of the second. The lower part shows the VHL mutation detected in a clear cell renal cell carcinoma that consists of the deletion of one cytosine residue. (Courtesy of Prof Aldo Scarpa, Department of Pathology, University of Verona.)
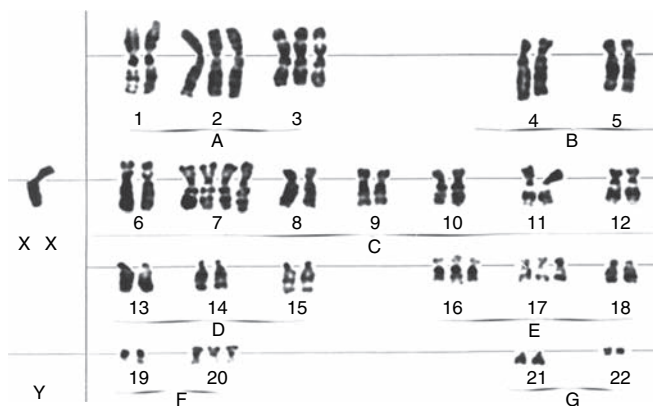
Figure 1.61

Papillary renal cell carcinoma: karyotype showing gain of chromosome 7.

Figure 1.62

Papillary renal cell carcinoma: interphase cytogenetics (FISH) showing three fluorescence signals for chromosome 7.
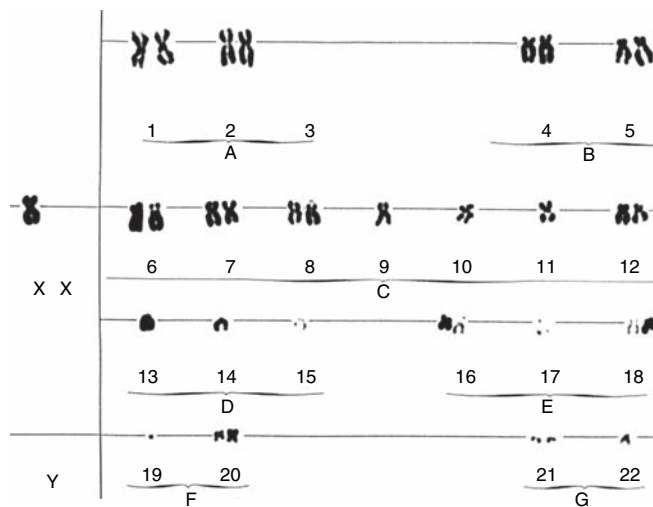
Figure 1.63

Chromophobe renal cell carcinoma: karyotyping showing multiple losses of chromosomes.

imbalance on 9p than type 1 cases.[108,109] The c-Met proto-oncogene mutation on chromosome 7 characterizes hereditary and a subset of sporadic papillary renal cell carcinomas.[101,110,111] Patients with the hereditary leiomyomatosis and renal cell cancer syndrome are at risk for cutaneous and uterine leiomyomas and solitary papillary renal

cell carcinoma with type 2 histologic features. Fumarate hydratase gene, the gene that causes this autosomal dominant syndrome, encodes fumarate hydratase, a Krebs-cycle enzyme.[112–114]

Chromophobe renal cell carcinoma is characterized by a combination of loss of chromosomes Y, 1, 2, 6, 10, 17, and 21 detected by classic cytogenetic analysis (Figure 1.63), loss of heterozygosity, comparative genomic hybridization, microsatellite markers, and fluorescent in situ hybridization (Figure 1.64).[115–118] Both classic and eosinophilic variants of chromophobe renal cell carcinoma share the same chromosomal losses.[119] Sarcomatoid chromophobe renal cell carcinomas are characterized by multiple chromosomal gains in both epithelial and sarcomatoid components.

Birt–Hogg–Dubè syndrome is a genodermatosis inherited as an autosomal dominant trait. This disorder is characterized by the

presence of multiple fibrofolliculomas on the skin of the head and neck accompanied by acrochordons and trichodiscomas.[120] Later, pulmonary cysts with spontaneous pneumothorax and multifocal renal tumors was recognized in patients affected by this syndrome. The most common renal tumor was a hybrid tumor showing combined zones of chromophobe renal cell carcinoma and oncocytoma patterns. The other tumors were chromophobe renal cell carcinoma (35%), clear cell renal cell carcinoma (9%), oncocytomas (5%), and papillary renal cell carcinoma (2%).[121,122]

The gene responsible for this syndrome has been localized on chromosome 17p11.2 by linkage analysis in Birt–Hogg–Dubè syndrome families and it encodes a protein called folliculin.[123,124] Although the progression oncocytoma/chromophobe renal cell

carcinoma seems highly suggestive in renal tumors occurring in patients with Birt–Hogg–Dubè syndrome, some data obtained from sporadic chromophobe renal cell carcinomas, sporadic oncocytomas, and renal oncocytosis in patients without Birt–Hogg–Dubè syndrome are not in accord with this hypothesis.[122,123,125]

Collecting duct renal carcinoma shows a high frequency (60%) of loss of heterozygosity in 1q32.1–32.2 by microsatellite analysis; others have shown monosomies for chromosomes 1, 6, 14, 15, and 22.[48,126]

Renal oncocytoma falls into three categories, namely characterized by normal karyotype (Figures 1.65 and 1.66), monosomy of chromosomes 1 and/or 14, often with Y chromosome loss, and structural abnormalities of 11q13 (Figure 1.67).[119,127–130]

Renal oncocytomatosis is a rare condition described by Warfel and Eble in 1982.[131] It is characterized by the presence of numerous bilateral oncocytomas and oncocytic changes in the renal tubules. Tickoo et al reported a group of patients with multiple oncocytic lesions and they called this disease oncocytosis. Some of these tumors had a morphology hybrid between oncocytoma and chromophobe renal cell carcinoma, suggesting that these neoplasms can be related and that chromophobe renal cell carcinoma can represent a progression from oncocytoma.[122]

No consistent cytogenetic anomalies have been demonstrated in *metanephric adenoma.* However, it has been shown that metanephric adenoma lacks the gains of chromosomes 7 and 17 and the loss of Y that are typical of papillary renal cell carcinoma and papillary adenoma; these data suggest that the supposed relationship between metanephric adenoma and the papillary renal cell neoplasms is missing.[132]

Angiomyolipoma can be sporadic or occurring in patients with tuberous sclerosis, a syndrome due to losses of *TSC1* (9q34) or *TSC2* (16p13.3) genes. Tuberous sclerosis is a complex disease characterized by mental retardation, seizures, and cellular proliferation, including angiomyolipomas, subependymal giant cell tumors, cutaneous angiofibromas, cardiac rhabdomyomas, lymphangioleiomyomatosis, and pulmonary multifocal micronodular hyperplasia.[62,133–135]
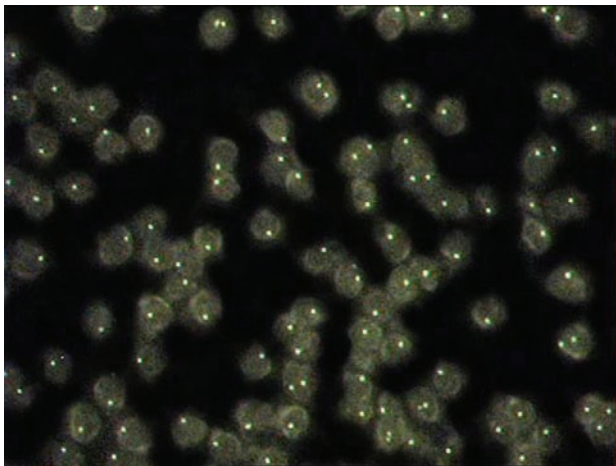
Figure 1.64
Chromophobe renal cell carcinoma: interphase fluorescence in situ hybridization analysis showing loss of chromosome 17 in neoplastic nuclei.
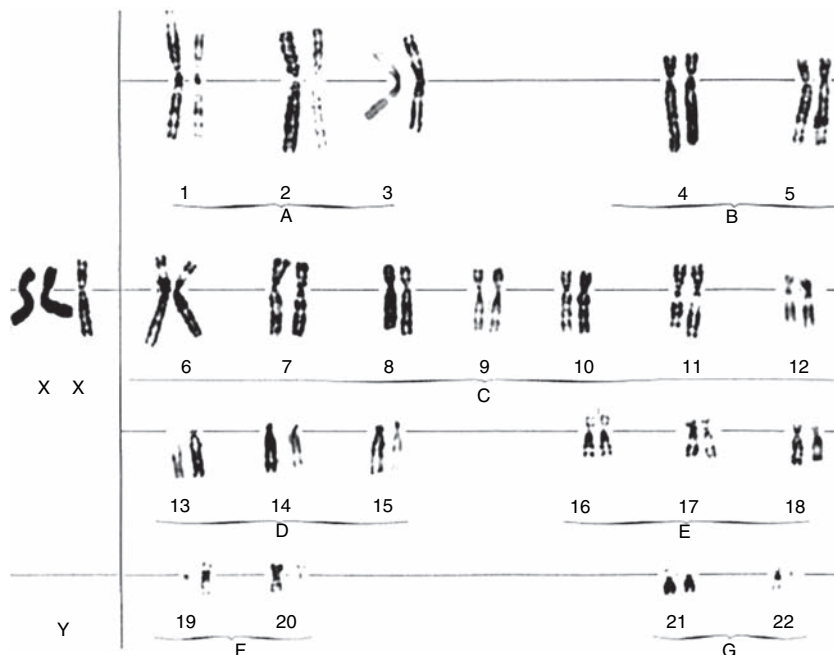
Figure 1.65
Renal oncocytoma: tumor showing normal karyotype pattern.
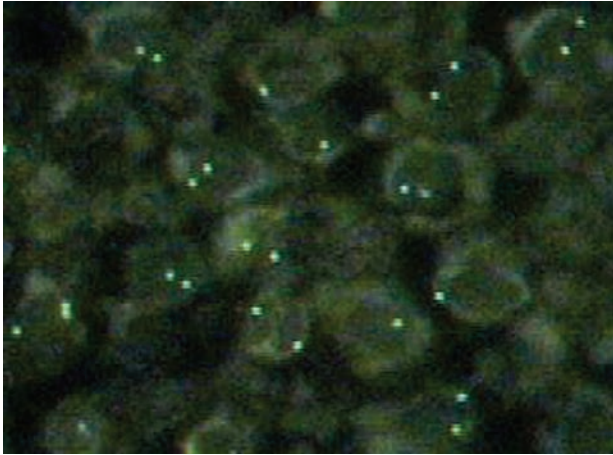
Figure 1.66
Renal oncocytoma: interphase fluorescence in situ hybridization showing two fluorescent signals on neoplastic nuclei for chromosome 6.
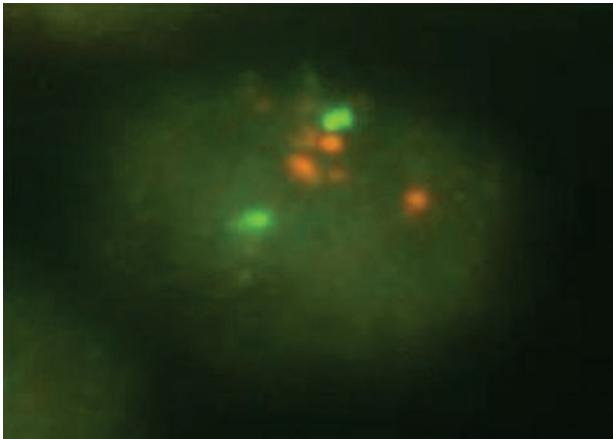
Figura 1.67
Renal oncocytoma: 11q13 genetic rearrangement by interphase cytogenetic using break-apart probes (SpectrumOrange and SpectrumGreen probes spanning the 11q13 region).
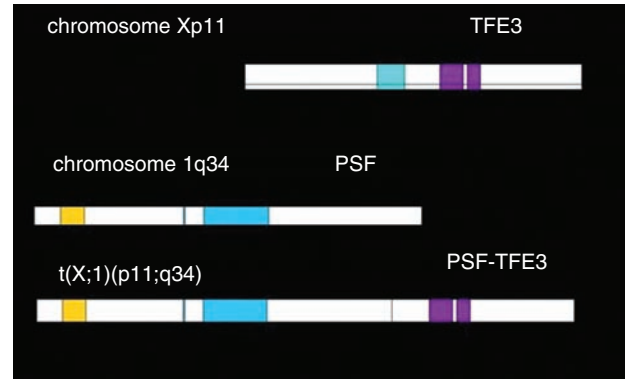
Figure 1.68
Renal cell carcinoma with Xp11 translocation: an example of t(X;1)(p11.2;q34), fusing the PSF and TFE3 genes.

Renal carcinomas with Xp11 translocations have different types of translocation occurring in this chromosomal region. The most common Xp11.2 translocations are the t(X;1)(p11.2;q21), which fuses the *PRCC* and *TFE3* genes, and the t(X;17)(p11.2;q25), which fuses the *ASPL* and *TFE3* genes. Other translocations are the t(X;1) (p11.2;p34), fusing the *PSF* and *TFE3* genes (Figure 1.68), the inv (X)(p11;q12), fusing the *NonO* (*p54nrb*) and *TFE3* genes, and the t(X;17)(p11.2;q23), fusing the *CLTC* and *TFE3* genes.[72,73,136,137]

Data regarding *mucinous tubular spindle cell carcinomas* indicate various chromosomal losses and gains, but no loss of 3p or trisomy 7 and/or trisomy 17.[80,81,138,139]

Fluorescence in situ hybridization analyses of *acquired cystic disease-associated renal cell carcinoma* with centromeric probes showed nuclei with three hybridization signals for chromosomes 1, 2, and 6, but not for chromosomes 10 and 17, whereas no genetic data are available regarding clear cell papillary renal cell carcinoma of the end-stage kidneys.[44,140]

Part 4

Differential diagnosis and use of ancillary methods for diagnosis

Adequate sampling and a good understanding of the morphologic features observed in the renal tumors usually minimize errors in their recognition and diagnosis. Nonetheless, the distinction of individual types, particularly in the category of renal cell neoplasms, can sometimes be very difficult because of the overlapping morphologic features, including variable cytoplasmic staining and architectural patterns. This can be a problem in core needle biopsies of renal masses (Figure 1.69), a procedure that is being increasingly performed with the advent of new minimally invasive forms of therapies, such as cryotherapy and diathermocoagulation, which require a preoperative diagnosis.

The major differential diagnoses based on the common histologic features include those tumors which display light-staining cytoplasm, those with eosinophilic granular cytoplasm, and those with papillary, tubular, or tubulopapillary architecture. The first group of neoplasms includes clear cell renal cell carcinoma, chromophobe renal cell carcinoma, renal carcinomas associated with Xp11.2 and 6,11 translocations, clear cell papillary renal cell carcinoma in end-stage kidneys, and epithelioid angiomyolipoma. The second group gathers the eosinophilic variant of chromophobe renal cell carcinoma, renal oncocytoma, clear cell renal cell carcinoma with large areas showing granular cytoplasm, renal carcinoma associated with t(6;11), acquired cystic disease-associated renal cell carcinoma, oncocytoma-like angiomyolipoma, and epithelioid angiomyolipoma. The third group collects papillary renal cell carcinoma, metanephric adenoma, mucinous tubular spindle cell carcinoma, and collecting duct carcinoma.

In order to further define ambiguous cases falling in the groups previously mentioned, it is necessary to apply new ancillary methods such as immunohistochemical and cytogenetic analyses.

In the recent literature numerous new immunohistochemical markers have been studied in the different renal histotypes and a large amount of data have been collected on this topic.

Among the broad spectrum of immunomarkers suggested in the literature, we propose a panel including CD10, parvalbumin, antiracemase, cytokeratin 7, and S100A1 (Figures 1.70 and 1.71)[141]

as the most promising and accurate diagnostic. HMB45 and, in particular circumstances, WT1, TFE3, and TFEB can be useful.

CD10 is a cell surface metalloproteinase, expressed by hematolymphoid and non-hematolymphoid tissues including the normal proximal nephron. It can be recognized in the majority of clear cell and papillary renal cell carcinomas, and a minority of chromophobe renal cell carcinomas and oncocytomas, and therefore may be useful in the distinction between these tumor types.[142–144]

Figure 1.69
Renal biopsy of a cortical renal mass: 1.4 cm core biopsy of neoplastic renal tissue available in formalin-fixed and paraffin-embedded tissue.
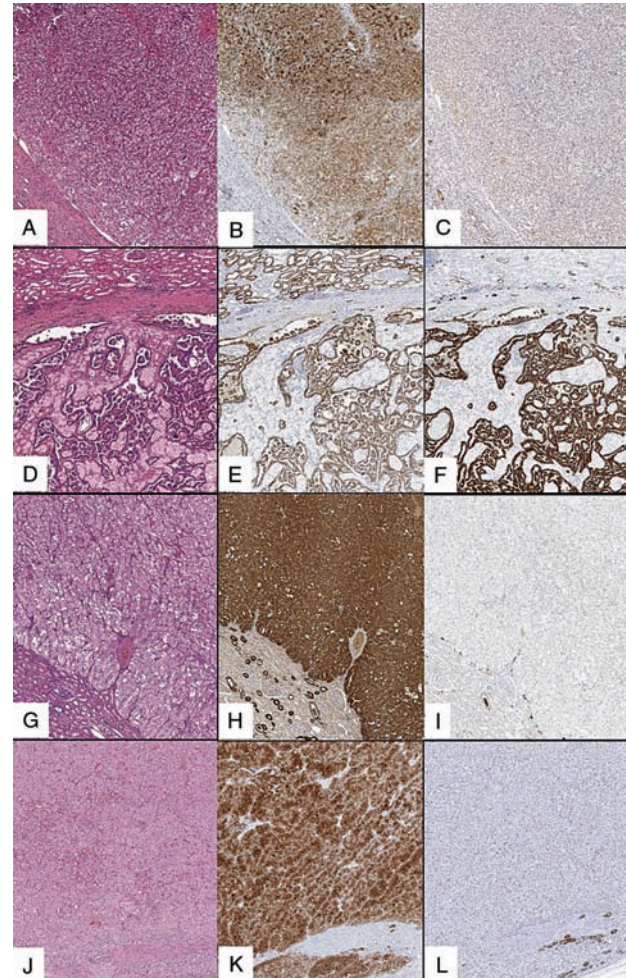
Figure 1.70
Renal cell epithelial neoplasms (major histotypes): immunohistochemical panel including CD10, parvalbumin, racemase, CK7, and S100A1. Clear cell renal cell carcinoma (A), CD10+ (B), PV− (C), papillary renal cell carcinoma (D), CD10+ (E), CK7+ (F), chromophobe renal cell carcinoma (G), PV+ (H), S100A1 − (I), renal oncocytoma (J), PV+ (K), CK7− (L).

Histotype	CD10	Parvalbumin (PV)	Anti-racemase	Cytokeratin 7 (CK7)	S100A1
Clear cell	+	–	– / +	–	+ / –
Papillary	+ / –	–	+	+	+ / –
Chromophobe	– / +	+	–	+ / –	–
Oncocytoma	–	+	–	– / +	+

Figure 1.71
Immunohistochemical panel suggested in routine differential diagnosis of the most frequent renal epithelial histotypes.

Parvalbumin is a cytosolic calcium-binding protein that is localized to the normal distal nephron. It is present in all chromophobe renal cell carcinomas and in a large percentage of oncocytomas[142] and acquired cystic disease-associated renal cell carcinomas, but it is constantly absent in clear cell and papillary renal cell carcinomas.[50,145–147]

Antiracemase stained all the papillary renal cell carcinomas and is almost constantly absent in metanephric adenomas, oncocytomas, and clear cell and chromophobe renal cell carcinomas.[148–150] However, mucinous tubular and spindle cell carcinomas and acquired cystic disease-associated renal cell carcinomas are positive for this marker.[44,138,151]

CK7 is commonly expressed by papillary and chromophobe renal cell carcinomas and clear cell papillary renal cell carcinomas in end-stage kidneys, whereas a limited number of oncocytomas can show immunoreactivity for this marker in scattered neoplastic cells.[146] Finally CK7 expression is very limited in clear cell renal cell carcinoma.[27,152]

S100A1 is another calcium-binding protein whose expression seems very useful in the differential diagnosis between chromophobe renal cell carcinomas and oncocytomas. Ninty-two percent of oncocytomas are positive for this marker, whereas 96% of chromophobe renal cell carcinomas do not stain for it.[153] The Wilms' tumor (WT) gene WT1 encodes a transcription factor demonstrated to be expressed in metanephric adenoma, but not in papillary renal cell carcinoma or mucinous tubular spindle cell carcinoma.[149,154] HMB45 is a well-recognized marker for all the variants

of angiomyolipoma.[66,69,155] However, recently its expression has been demonstrated in carcinomas with t(6;11)[76] and rarely in those with Xp11 translocation.[156] In this particular differential diagnosis the immunohistochemical analysis with antibodies recognizing TFEB and TFE3 can be very useful.

The immunohistochemical method should be applied with particular attention because of the high levels of endogenous biotin found in normal renal parenchyma and numerous renal neoplasms. Moreover the use of a panel of antibodies is preferred over a single stain, and immunohistochemical results must be interpreted in light of the morphologic findings.

The classic cytogenetic analysis can be useful in the differential diagnosis of particular tumors.[99] However, it is limited for practical histopathologists and this method has to be applied at the beginning of the study of every renal tumor in the routine practice. Recently, fluorescence in situ hybridization on formalin fixed, paraffin embedded tissues, using centromeric probes to evaluate the gains and losses of the chromosomes, has been proposed as a useful diagnostic tool in selected diagnostic problems such as oncocytoma versus chromophobe renal cell carcinoma,[119] papillary renal cell neoplasms versus metanephric adenoma, or mucinous tubular spindle cell carcinoma, and acquired cystic disease-associated renal cell carcinoma,[132,138] and the other tumors with pink granular cytoplasm (oncocytoma, eosinophilic variant of chromophobe renal cell carcinoma, papillary renal cell carcinoma type 2, and clear cell renal cell carcinoma with extensive granular areas).[44]

Part 5

Principles of staging and grading

Staging

In 1958 Flocks and Kadesky proposed the first classification of renal cell carcinoma according to the anatomic extension of tumors: tumors limited to the renal capsule (stage I), invasion of the renal pedicle and/or renal fat (stage II), regional lymph node involvement (stage III), and demonstrable distant metastasis (stage IV).[157,158]

In 1969 Robson et al proposed a new staging system grouping all localized renal cell carcinomas in a single group (stage I) and distinguished the tumors infiltrating perirenal fat (stage II), involving the gross renal vein or inferior vena cava (stage 3A), or lymph nodes (stage 3B), from those extending outside the Gerota's fascia (stage IVA) or with distant metastasis (stage IVB).[159]

This staging system was widely used until the early 1990s, when it was progressively replaced by the tumor nodes metastasis (TNM) system proposed by the Union International Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC).

Renal cell carcinoma found a place in the second edition of TNM published by the UICC in 1974. Figure 1.72 summarizes the main changes adopted by UICC/AJCC to obtain a better patient stratification and to distinguish more efficaciously subgroups of patients with different prognoses.[159a] Figure 1.73 shows the TNM stage grouping according to the latest 2002 version.[159b]

The latest version of the TNM staging system introduced a subclassification of stage I renal cell carcinoma into two subgroups, applying the breakpoint of 4 cm: T1a ≤4 cm; T1b >4 cm but ≤7 cm. This update was mainly aimed at an easier clinical identification of the patients suitable for elective nephron-sparing surgery. In 1999, Hafez et al published the data on 485 patients who had undergone nephron-sparing surgery at the Cleveland Clinic, reporting 10-year cancer-specific survival rates of 90% for patients in the ≤4 cm subgroup, 71% in the 4.1–7 cm and 62% subgroup, >7 cm.[158]

This issue had been assuming a greater relevance, considering the major increase in the percentage of incidentally detected kidney cancers, which paralleled the higher number of ≤4 cm renal cell carcinomas suitable for elective nephron-sparing surgery. A recent multicenter, multinational, European study showed that the 2002 TNM version allowed stratification of localized renal cell carcinomas

Tumor classification	1987 TNM	1997 TNM	2002 TNM
T1	Tumor ≤ 2.5 cm, limited to kidney	Tumor ≤ 7 cm, limited to kidney	
T1a			Tumor ≤ 4 cm, limited to kidney
T1b			Tumor > 4 cm ≤ 7 cm, limited to kidney
T2	Tumor > 2.5 cm, limited to kidney	Tumor > 7 cm, limited to kidney	Tumor > 7 cm, limited to kidney
T3	Tumor extends into major veins or invades adrenal or perinephric tissues but not beyond Gerota's fascia	Tumor extends into major veins or invades adrenal or perinephric tissues but not beyond Gerota's fascia	Tumor extends into major veins or invades adrenal or perinephric tissues but not beyond Gerota's fascia
T3a	Perinephric or adrenal extension	Perinephric or adrenal extension	Perinephric or adrenal extension
T3b	Renal vein involvement	Renal vein or vena cava involvement below diaphragm	Renal vein or vena cava involvement below diaphragm
T3c	Vena cava involvement below diaphragm	Vena cava involvement above diaphragm	Vena cava involvement above diaphragm
T4		Outside Gerota's fascia	Outside Gerota's fascia
T4a	Outside Gerota's fascia		
T4b	Vena cava involvement above diaphragm		

Figure 1.72
Tumor classification in TNM staging systems for renal cell carcinoma.

Stage	T	N	M
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3 T1,T2,T3	N0 N1	M0 M0
Stage IV	T4 Any T Any T	N0,N1 N2 Any N	M0 M0 M1

Figure 1.73
TNM stage grouping according to 2002 version.
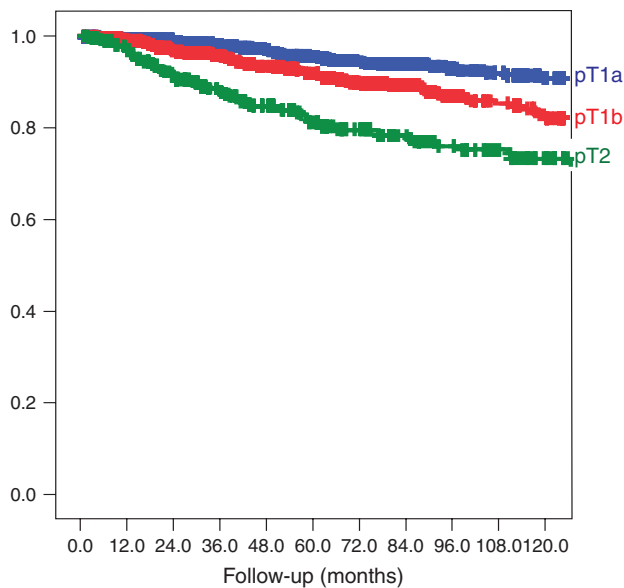
Figure 1.74
Comparison of disease-specific survival probabilities stratified by pathologic status (2002 TNM version). The 10-year disease-specific survival probabilities were 91% for patients with pT1a, 83% for patients with pT1b, and 75% for patients with pT2 (from Cancer 2005; 104: 968–74).[160]

into subgroups with significantly different disease-specific survival rates[160] (Figure 1.74).

The pathologic stage of renal cell carcinoma is the most important predictor of survival. Five-year cause-specific survival of patients with localized disease has been reported to range from 90 to 100% for stage I (T1N0M0) and from 74 to 95% for stage II (T1N0M0).[161–163] Survival data from a multicenter European study showed that 5-year and 10-year disease-specific survival probabilities were 95.3% and 91.4%, respectively, for patients with pT1a tumors; 91.4% and 83.4%, respectively, for patients with pT1b tumors, and 81.6% and 75.2%, respectively, for patients with pT2 tumors (log rank p value <0.0001). Moreover, this study demonstrated that the application of the 2002 TNM staging system allowed statistically significant stratification of the cancer-related outcome in the subgroup of patients with clear cell renal cell carcinoma (log rank p value <0.0001). Conversely, the 2002 TNM staging system did not appropriately stratify the cancer-related outcome of the patients with papillary renal cell carcinoma (log rank p value = 0.08).[163]

The invasion of perinephric or renal sinus fat and/or the ipsilateral adrenal gland, renal vein or inferior vena cava involvement,

and the presence of metastasis in a single lymph node (stage III) significantly worsen prognosis. The 5-year cause-specific survival of patients with stage III renal cell carcinoma ranges from 60 to 70%.[161,164] In particular, perinephric or renal sinus fat invasion causes a 15–20% reduction in survival in comparison with organ-confined tumors. In this subgroup of patients, 5-year cancer-specific survival decreases to 51–68%.[163,164]

Neoplastic extension to the renal vein or to the inferior vena cava is found in 10–20% and 4–10% of the cases, respectively. In a high number of patients, venous involvement is associated with the simultaneous presence of local invasion by the primary tumor and involvement of regional lymph nodes. Moreover, cranial extension of the tumor thrombus into the vena cava is reported to be associated with a higher probability of metastatic spread.

Complete removal of the tumor thrombus in patients without other prognostic factors is associated with 5-year cause-specific survival rates of 47–68%. Survival rates dramatically decrease in the patients with positive lymph nodes or distant metastases to figures lower than 20%. An additional negative prognostic factor in this stage of the disease is the infiltration of the venous wall by the neoplastic thrombus. In this subcategory of patients the 5-year cancer-specific survival is reduced to 25%. However, surgical removal of the caval infiltrated segment could increase the 5-year survival rate to 57%.[163–165]

The involvement of regional lymph nodes affects survival more than previous anatomic prognostic factors. The 5-year cancer-specific survival rate in patients with lymph node involvement is only 8–35%. Metastatic spread of the disease is the worst prognostic factor. The 5- and 10-year cancer-specific survival rates are 5–10% and 0–7%, respectively. Patients with a single metastasis have a better long-term prognosis.[166,167]

Despite all the implemented and proposed modifications, the optimal stratification of renal cell carcinoma patients in the context of the TNM staging system is still controversial, both for localized and locally advanced tumors.

Some authors proposed an ideal breakpoint ranging from 4.5 to 5.5 cm to stratify outcomes in patients with confined renal cell carcinoma.[166] Moreover, in addition to tumor size, data supported the integration of symptoms into the primary tumor classification. Data from a multicenter European database, which analyzed clinical records of 1138 patients with a mean follow-up duration of 87 months after partial or radical nephrectomy, showed that confined renal cell carcinoma should be subdivided into three subgroups according to tumor size and mode of presentation:

1. patients with ≤5.5 cm incidentally detected renal cell carcinoma (Figure 1.75);
2. patients with ≤5.5 cm symptomatic renal cell carcinoma; and
3. patients with >5.5 cm renal cell carcinoma.
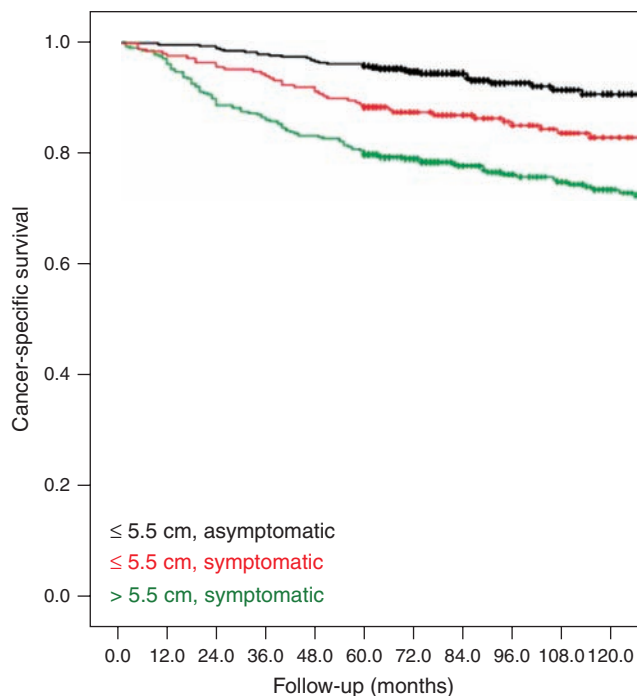
Figure 1.75

Cancer-specific survival stratified by the 5.5 cm tumor size and symptom classification. The 10-year cancer-specific survival probabilities were 91% in the first group (black curve), 83% in the second group (red curve), and 73.5% in the third group (green curve) (from Cancer 2005; 15: 104: 2116–23).

The authors proposed changing the classification of localized renal cell carcinoma according to this last finding.[168]

Moreover, refinements remain to be performed for pT3 tumors. Local tumor extension into the ipsilateral adrenal gland is currently classified as pT3a, as well as renal cell carcinoma invading perinephric or renal sinus fat. Many studies suggested that renal cell carcinoma with direct ipsilateral adrenal invasion behaved more aggressively than tumors involving perinephric or renal sinus fat.[169] Moreover, the renal cell carcinomas invading the adrenal gland had similar outcomes to those of the patients with tumors extending beyond Gerota's fascia or into adjacent organs. Recently, it has been proposed to classify them as pT4.[170,171]

For renal sinus fat invasion only, it has not been established whether this carries the same prognostic information as does perinephric fat invasion. The renal sinus contains a large number of veins and lymphatics. Tumor invasion into this compartment might permit a higher potential dissemination compared to the extension into the perinephric fat, where veins and lymphatics are less abundant.[172]

A recent analysis of 205 patients without direct adrenal invasion, who had undergone radical nephrectomy for pT3a clear cell carcinoma, highlighted that tumors invading the renal sinus fat were more aggressive than those with perinephric fat involvement.[169]

Another critical point in the TNM classification concerns patients with venous involvement. The 2002 TNM version does not distinguish between patients with tumor thrombus involving the renal vein only, and those with inferior vena cava tumor thrombus below the diaphragm (pT3b). In a series of 422 pT3b patients, Leibovich et al demonstrated that patients with thrombus involvement of the renal vein only were less likely to die from renal cell carcinoma

than patients harboring a larger tumor thrombus burden.[171] Moreover, the primary tumor classification made no distinction according to the level of IVC thrombus below the diaphragm. Data from Moinzadeh and Libertino showed that the level of tumor thrombus into the inferior vena cava did not significantly affect long-term survival.[172] The most relevant finding regarding venous involvement is that patients with tumor thrombus in the inferior vena cava below the level of the diaphragm have a significantly decreased survival compared to those with tumor thrombus in the renal vein.

Even the classification of the lymph node (N) parameter has undergone several changes over the years. The most important controversy concerned the ability to stratify patients with lymph node involvement in different prognostic categories. The 2002 regional lymph node classification for renal cell carcinoma is based on the number of positive hilar, abdominal para-aortic, and paracaval lymph nodes that are identified during lymphadenectomy. However, some authors suggested that outcome is not significantly different between patients with pN1 and pN2 disease.[173,174]

Recently, Terrone et al proposed reassigning pN substratification according to either a cut-off of four positive lymph nodes or 60% lymph node density.[174] In contrast, the Mayo Clinic team suggested that notation regarding the presence or absence of extranodal extension improves the prognostic accuracy of the current regional lymph node classification. In fact, extranodal extension provides prognostic information in carcinomas at other sites such as breast, head, and neck.[173]

For adequate M-staging of patients with renal cell carcinoma the abdominal CT and MRI are recommended. Moreover, a plain chest X-ray can be sufficient for assessment of the lung in low-risk patients also if chest CT is considered most sensitive. Bone scan and brain CT are indicated only in symptomatic patients.[175]

Grading

In 1932, Hand and Broders were the first to report a relationship between histologic grade and cancer-specific survival in patients with renal cell carcinoma, showing that patients with high-grade renal cell carcinoma were more likely to die, and died sooner after diagnosis than those with low-grade tumors.[175a] After the proposals of Arner et al in 1965, Skinner et al in 1971, and Syrjanen and Hjelt in 1978, Fuhrman et al proposed a new grading system in 1982.[176] The system was based exclusively on the nuclear features of renal cell carcinoma cells. Figure 1.76 summarizes the characteristics of the different grading systems available in renal cell carcinoma.

The Fuhrman nuclear grading system is used by most uropathologists in North America and Europe. Such widespread diffusion and popularity are attributable primarily to the system's simplicity and its proven correlation with other pathologic variables. This four-tiered grading system is essentially based on nuclear size and morphology and on the presence or absence of nucleoli.

Grade 1 tumors consist of cells with small (approximately 10 μm), round, uniform nuclei with inconspicuous or absent nucleoli (Figure 1.77); Grade 2 tumors have larger nuclei (approximately 15 μm) with irregular morphology and small nucleoli when examined under high power (×400 magnification); Grade 3 tumors have even larger nuclei (approximately 20 μm) with irregular outlines and large, prominent nucleoli that are evident even at low power (×100 magnification); and Grade 4 tumors differ from Grade 3 lesions in that they contain bizarre, multilobed nuclei and heavy chromatin clumps (Figure 1.78).

Arner system (1965)
- grade 1: Well differentiated, well demarcated, no polymorphism
- grade 2A: Moderately differentiated, locally circumscribed, not necessarily capsulated
- grade 2B: Poorly circumscribed but not infiltrating, marked polymorphism, mitoses present
- grade 3: Poorly differentiated, markedly pleomorphous, infiltrating, tumor found in capillaries

Skinner system (1971)
- grade 1: small nuclei, indistinguishable from normal tubular cell nuclei
- grade 2: slightly irregular, frequently pyknotic, but no nucleoli
- grade 3: large, irregular, pleomorphic nuclei with prominent nucleoli
- grade 4: extremely bizarre nuclei

Syrianen and Hjelt system (1978)
- grade 1: spherical nuclei of equal size, delicate chromatin, inconspicuous nucleoli, rare mitoses
- grade 2: slightly larger spherical nuclei with distinct nucleoli and a few scattered mitoses
- grade 3: prominent anisonucleosis and nucleoli, frequent mitoses
- grade 4: many bizarre nuclei and frequent mitoses; frequent spindle-shaped cells
Each of the above categories is divided into "A", well demarcated and "B", poorly demarcated

Fuhrman nuclear grading system (1982)
- grade 1: tumor cells with small (approximately 10 μm), round nuiform nuclei without nucleoli
- grade 2: tumor cells with larger nuclei (approximately 15 μm), with irregularities in
         outline and nucleoli when examined under high power (400 x)
- grade 3: tumor cells with even larger nuclei (approximately 20 μm), with an obviously irregular
         outline and prominent larger nucleoli even at low power (100 x)
- grade 4: tumor cells with bizarre, multilobed nuclei and heavy clumps of chromatin

Thoenes system (1986)
- grade 1: small nuclei, similar to normal tubular cell nuclei; chromatic delicate or condensed up to pyknosis
- grade 2: larger nuclei, varying moderately in size and shape
- grade 3: highly enlarged nuclei, polymorphous or spindle-shaped, varying in size up to giant nuclei. Chromatin highly coarsened
         Single or multiple nucleoli, mostly extremely enlarged. Frequent mitoses, often atypical

Delahunt ad Nacey system (1987)
- grade 1: small nucleus, uniform in size and shape; small nucleolus, round and basophilic
- grade 2: moderate grade of variation in nucleous size and shape, with some angularity of the nuclear margins; chromatin
         clumping at the nuclear membrane. Brightly eosinophilic nucleolus prominent within the nucleus
- grade 3: pronounced variation in nucleus size, with giant forms and/or multinucleate tumor giant
         cells. Large and angulated nucleolus, with multiple nucleoli in the same nucleous

Mayo Clinic "standardized nuclear grade" (2000)
- grade 1: tumor cells with small, round nuclei, with inconspicuous nucleoli (visible at 400x)
- grade 2: tumor cells with round to slightly irregular nuclei, with mildly enlarged nucleoli (visible at 200x)
- grade 3: tumor cells with round to irregular nuclei, with prominent nucleoli visible at 100 x
- grade 4: tumor cells with enlarged, pleomorphic or giant cells.

Figure 1.76
Grading systems proposed for renal cell carcinoma. Reproduced with permission from Novara G, Martignoni G, Artibani W, Ficarra V. Grading systems in renal cell carcinoma. J Urol 2007; 177 (2): 430–6.
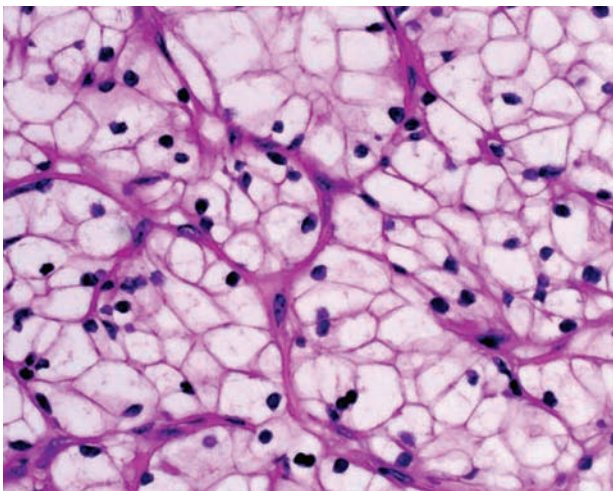
Figure 1.77
Clear cell renal cell carcinoma. Fuhrman Grade 1.

Figure 1.79 summarizes cancer-specific survival probabilities stratified by tumor grades as reported in the most relevant published papers. In 2000, Tsui et al reported on 643 renal cell carcinoma patients treated at UCLA with both radical and partial nephrectomy, finding significant survival differences both between grade 1 and grade 2 and between grade 2 and grade 3–4 tumors. In addition, the paper confirmed the correlation of nuclear grade and pathologic stage, there being 91% of grade 1 or 2 renal cell carcinomas in stage I and 61% of grade 3 or 4 cancer in stage IV, respectively.[177]

In 2001, Ficarra et al analyzed 333 patients who had undergone radical nephrectomy for renal cell carcinoma and confirmed the correlation between Fuhrman nuclear grade and the other pathologic variables, such as pathologic stage of the primary tumor, pathologic lymph node involvement, presence of metastases, and invasion of the venous system. Moreover, the authors showed that the survival probabilities of grade 1 and grade 2 tumors were overlapping, while a significantly different outcome was registered between grade 1–2, grade 3, and grade 4 neoplasms.[178]

Similar survival figures were reported by Frank et al, who analyzed 1801 patients treated at the Mayo Clinic for clear cell renal cell
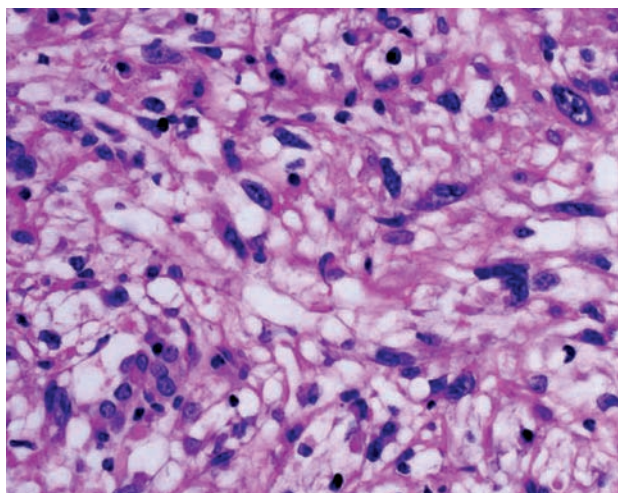
Figure 1.78
Clear cell renal cell carcinoma. Fuhrman Grade 4.

carcinoma. After a mean follow-up period of almost 10 years, the authors showed similar survival rates for grade 1 and 2 tumors, which were significantly better than those of grade 3.[179]

No paper showed unequivocally the independent predictive value of nuclear grading systems regardless of pathologic tumor stage until 2000, when the UCLA team reported a multivariate analysis of the prognostic factors in renal cell carcinoma using the Cox proportional hazard model. The authors generated a multivariate model including Eastern Cooperative Oncology Group performance status, stage of the primary tumor according to the 1997 TNM staging system, overall TNM pathologic stage, and nuclear grade. The Fuhrman nuclear grading system, after clustering grades 3 and 4, proved to be an independent predictor of cancer-specific survival ($p < 0.001$) as well as the overall 1997 pathologic stage ($p < 0.001$).[177]

In 2001, Ficarra et al reported a multivariate model including only pathologic variables. The Fuhrman nuclear grading system proved significant after grouping grades 1 and 2 ($p = 0.002$), and T stage ($p < 0.0001$), N stage ($p = 0.009$), and M stage ($p < 0.0001$) were also statistically significant.[178]

In 2002, the Mayo Clinic team provided a Cox proportional hazard model using bootstrap methodology. Also in this case after combining grades 1 and 2, nuclear grading turned out to be an independent predictor of cancer-specific survival, with a risk ratio of 1.50 ($p < 0.001$) and 3.01 ($p < 0.001$) for grades 3 and 4, respectively.[179]

References	Cases	Histological subtype	5-year survival probabilities (%)				Grades clustering
			G1	G2	G3	G4	
Fuhrman, 1982	103	All	65	30	32	10	1 Vs 2-4
Medeiros, 1988	121	All	85	70	21	23	1-2 Vs 3-4
Grignon, 1989	103	All	88		80	43	1-2 Vs 3-4
Green, 1989	55	All	91			9	1-3 Vs 4
Munichor, 1992	79	All	50	55	10.5	14.3	1-2 Vs 3-4
Gelb, 1993	82	All	n.r.	n.r.	n.r.	n.r.	1-2 Vs 3-4
Bretheau, 1995	190	All	76	72	51	35	1-2 Vs 3-4
Usubuton, 1998	165	All	97	83	78	66	1-2 Vs 3-4
Tsui, 2000	643	All	89	65	46		1 Vs 2 Vs 3-4
Ficarra, 2001	333	All	94	86	59	31	1-2 Vs 3 Vs 4
Frank, 2002	1801	All	n.r.	n.r.	n.r.	n.r.	1-2 Vs 3 Vs 4
Minervini, 2002	213	All	96	87	60		1-2 Vs 3-4
Amin, 2002	405	All	100	94	80	35	1-2 Vs 3 Vs 4
Ficarra, 2003	1446	All	86.1	79.7	59.4	29.4	1 Vs 2 Vs 3 Vs 4
Cheville, 2003	1985	Clear cell	n.r.	n.r.	n.r.	n.r.	1-2 Vs 3 Vs 4
Cheville, 2003	270	Papillary	n.r.	n.r.	n.r.	n.r.	1-2 Vs 3 Vs 4
Mejean, 2003	88	Papillary	91		51		1-2 Vs 3-4
Ficarra, 2005 †	388	Clear cell	95.4	90.7	65.3	40	1-2 Vs 3 Vs 4
Ficarra, 2005 ‡	388	Clear cell	100	90.1	77.1	54.7	1-2 Vs 3 Vs 4
Patard, 2005	4063	All	89.1	72.1	49.8	28	1 Vs2 Vs 3 Vs 4

G1: grade 1; G2: grade 2; G3: grade 3; G4: grade 4
† original Fuhrman nuclear grading system.
‡ reviewed Fuhrman nuclear grading system.
n.r. not reported

Figure 1.79
Cancer-specific survival probabilities stratified by nuclear grade. Critical literature analysis. Reproduced with permission from Novara G, Martignoni G, Artibani W, Ficarra V. Grading systems in renal cell carcinoma. J Urol 2007; 177(2): 430–6.

To our knowledge, only a few papers have demonstrated a significant prognostic value for the Fuhrman system without clustering groups of patients with different grades.

Ficarra et al reported 1446 renal cell carcinomas treated with both radical nephrectomy and nephron-sparing surgery at two Italian urologic centers. The 5- and 10-year cancer-specific survival rates were 86.1% and 77.2% for grade 1, 79.7% and 67.7% for grade 2, 59.4% and 45.9% for grade 3, and 29.4% and 18.5% for grade 4 renal cell carcinoma, respectively. Patients with grade 1 had better survival rates than those with grade 2 renal cell carcinoma ($p = 0.02$). Similarly, the curve of grade 2 cancer was significantly different from that of grade 3 ($p < 0.0001$) and, likewise, the curve of grade 3 from that of grade 4 ($p < 0.0001$) tumors (Figure 1.80).

Multivariate analysis confirmed the independent predictive value of the Fuhrman nuclear grading system ($p < 0.001$), as well as of the pathologic stage ($p < 0.001$), pathologic size (vs >4 cm; $p = 0.003$), venous involvement ($p = 0.001$), and mode of presentation ($p = 0.001$). However, although the survival difference between grade 1 and grade 2 tumors was statistically significant, the data might be clinically irrelevant. The univariate analysis demonstrated only a 10% difference in 10-year cancer-specific survival, which might have turned out statistically significant only because of the extremely high number of censored cases rather than because of a clinically relevant difference.[5] Similarly, Patard et al published a large multicenter study, including more than 4000 patients from eight international, academic centers, from Europe and the USA. The study was focused on the assessment of the independent predictive value of tumor histologic subtypes. In univariate analysis, Fuhrman nuclear grades were statistically significant, with 5- and 10-year cancer-specific survival rates of 89.1% and 81% for grade 1; 72.1% and 56.5% for grade 2; 49.8% and 30.1% for grade 3; and

28% and 18.8% for grade 4 tumors ($p = 0.0001$). Moreover, the Fuhrman nuclear grading system was shown to be an independent predictor of cancer-specific survival in multivariate analysis, as well as TNM stage and ECOG performance status.[180]

The reported 5-year cancer-specific survival probabilities according to Fuhrman nuclear grading are extremely variable: 50 to 100% in grade 1; 30 to 94% in grade 2; 10 to 80% in grade 3, and 9 to 66% in grade 4 tumors. The wide variability of the reported data could be explained in several ways.

First of all, many authors pointed out the moderate interobserver reproducibility of the Fuhrman nuclear grading system. Lanigan et al were the first to analyze the level of agreement among four pathologists assigning renal cell carcinoma grades according to four different systems (Arner, Skinner, Syrjanen-Hjelt, and Fuhrman systems). The interobserver agreement was shown to be moderate for all systems.[181]

In the larger study in the field, Lohse et al compared original nuclear grades assigned at the moment of the initial pathologic diagnosis to the standardized grades reassigned after slide review of more than 2000 cases at the Mayo Clinic. The paper provided separate analyses for clear cell, papillary, and chromophobe renal cell carcinomas. Among clear cell renal cell carcinoma, the nuclear grade remained unchanged on review in 56.3% of cases, while it was upshifted in 35.2% by one or more grades and downshifted in 8.4%. Among papillary histologic subtypes, 49% of original grades were reconfirmed, while 44.1% and 6.8% were upshifted and downshifted, respectively. Similarly, among chromophobe tumors, 55%, 38%, and 7% were confirmed, upgraded, and downgraded on review, respectively. More importantly, the authors demonstrated for each histologic subtype that the revised nuclear grades were powerful predictors of cancer-specific survival, also after adjusting for the 1997 TNM stage.[182]

In a similar European study, Ficarra et al compared original and reviewed Fuhrman nuclear grading in a series of 388 conventional clear cell renal carcinomas. The concordance was moderate, with original grade 1 tumors upshifted by one grade in 38.7% of cases, by two in 18.9%, and by three in 2.7%. The original grade 2 tumors were upgraded by one grade in 34% of cases and by two in 4.3%. Original grade 3 and grade 4 tumors remained unchanged in 73.1% and 89.3% of cases, respectively.[183]

Again, the variability of the cancer-specific survival probabilities stratified by grade could depend on the heterogeneity of renal cell carcinoma, which often presents areas with different grades in the same tumor. Al-Aynati et al reported the presence of more than one grade even in 53% of cases, with heterogeneity being the rule more than the exception.[184] Hence, some pathologists would upgrade a grade 2 tumor according to a small focus of higher grade nuclei detected at high power, while others would resist this temptation. Although nuclear grade should be based on the worst identified area, there is still a lack of consensus about the minimal size in order to be considered significant. The Mayo Clinic group proposed recording the highest grade occupying at least one high-power field.[182]

Thirdly, suboptimal tissue fixation, different fixation solution, and fixation protocols can markedly affect nuclear grading attribution. After suboptimal fixation, Goldstein reported nucleoli disappearance and chromatin modification being coarser and less hyperchromatic, which might cause grade migration.[185]

An additional explanation of the variability of the reported cancer-specific survival probabilities is the histotype. Although UICC and AJCC recommended assignment of nuclear grades only in clear cell and papillary renal cell carcinomas, most of the papers presented data on series including all histologic subtypes of renal cell carcinoma, without stratification.
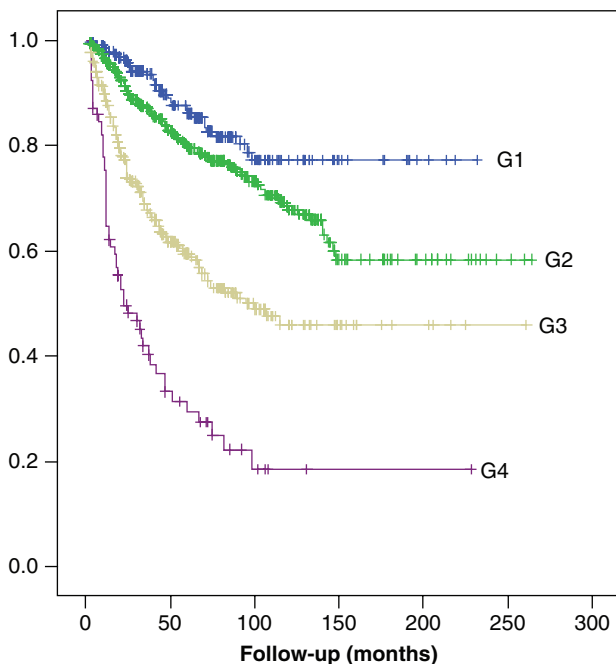
Figure 1.80

Cancer-specific survival probabilities according to Fuhrman nuclear grade. Analysis performed on 1188 renal cell carcinoma patients who undergone radical or partial nephrectomy at Verona and Padua University (Italy).[5] (G1=blue; G2=green; G3=Yellow; G4=Violet).

In a large series from the Mayo Clinic, Cheville et al underlined the survival difference among different histotypes. Stratifying by histologic subtype and nuclear grade, overlapping survival probabilities were shown between grade 1 and 2 tumors, regardless of tumor histologic subtype. Similarly, patients with grade 3 clear cell renal cell carcinoma had a worse outcome than both grade 3 papillary and chromophobe renal cell carcinomas, while the prognosis was poor for grade 4 renal cell carcinoma of any histologic subtype.[186]

With the intent to improve the prognostic accuracy of nuclear grade, nuclear morphometry has been developed. With the use of computer imaging technology, image-based morphometry aims at assessing quantitatively nuclear descriptor factors such as nuclear diameters, nuclear perimeter, nuclear area, roundness factor, and nucleolar area. Although a few papers have shown the prognostic relevance of nuclear morphometry, this methodology has not gained wide acceptance.

Other morphologic prognostic factors

Other important morphologic prognostic factors are histologic subtype, tumor necrosis, presence of sarcomatoid features, and collecting system invasion.

Histologic subtype

Although molecular studies have extensively clarified the existence of genetic differences among the different morphologic variants of renal cell carcinomas, the independent prognostic value of the histotype remains controversial (Figure 1.81).

In 1999, Ljungberg et al were the first to observe significantly different cancer-specific survivals in the three main renal cell carcinoma histotypes. In that series, patients with chromophobe renal cell carcinomas had significantly longer survival, compared with the patients with conventional clear cell renal cell carcinomas, as did patients with papillary renal cell carcinoma.[187] Also Moch et al showed that patients with chromophobe renal cell carcinoma had a significantly improved prognosis, compared with patients with clear cell carcinoma. In contrast, they did not find significant differences in outcome between patients with chromophobe and papillary renal cell carcinoma.[188] The prognostic role of the histologic subtype classification was also confirmed on univariate analysis by Amin et al in 2002. Nevertheless, in this study the histologic subtype did not turn out to be statistically significant on multivariate analysis.[189]

TNM stage, nuclear grade, and tumor necrosis were independent predictive factors of cancer-specific survival. A possible statistical explanation is that, given the predominance of clear cell renal cell carcinoma in most surgical series, differences in cancer-specific survival probabilities among the main histologic subtypes of renal cell carcinoma cannot be evaluated easily when stratified by tumor stage and nuclear grade. In a large series of 2528 patients from the Mayo Clinic, Cheville et al reported that patients with conventional renal cell carcinoma had a significantly poorer outcome, compared with patients with tumors of the two other types, even when the analysis was adjusted for TNM stage and nuclear grade. Also, in that series no survival difference was observed between papillary and chromophobe renal cell carcinoma.[186]

In 2005 Patard et al published a retrospective, multicenter study, analyzing 4063 patients surgically treated for renal cell carcinoma in

Author	Cases	Conventional RCC		Papillary RCC		Chromophobe RCC	
		%	5-year cancer-specific survival	%	5-year cancer-specific survival	%	5-year cancer-specific survival
Ljungberg, 1999	186	78%	43%	13%	61%	7%	91%
Moch, 2000	588	83%	50%	11%	---	5%	78%
Amin, 2002	405	68%	76%	20%	86%	6%	100%
Cheville, 2003	2,528	83.2%	68.9%	11.3%	87.4%	4.3%	86.7%
Beck, 2004	1,057	75%	73.3%	15%	81.7%	10%	80.1%
Patard, 2005	4,063	87.7%	63.8%	9.7%	69.8%	2.5%	83.9%
Gudbjartsson, 2006	629	88.7%	54.9%	8.4%	66.5%	2.1%	84.6%
Ficarra, 2006	470	79%	81.3%	11.6%	90.1%	5.1%	100%

Figure 1.81

Frequency of different histologic subtypes and cause-specific survival in the published series. Reproduced with permission from reference 190.

six European and two American centers. The authors of that study observed significantly higher cancer-specific survival for patients with chromophobe renal cell carcinoma than for patients with both papillary and conventional renal cell carcinoma. Disease-specific survival in the two main histologic subtypes proved to be similar, both in the subgroups of patients with localized as well as metastatic renal cell carcinoma. On multivariate analysis only pathologic stage, nuclear grading, and ECOG performance status were independent prognostic values. The authors recognized the absence of a centralized pathologic slide review as the main limitation of their study. In fact, even though every participating center had its diagnoses reported by a limited number of experienced uropathologists, it was not possible to state with certainty that the different centers used the same criteria in assigning the different histotypes.[180]

These two large studies have an important methodologic difference in the pathologic evaluation: in the paper from the Mayo Clinic, a single pathologist reviewed all the pathologic slides to reassign the histotype, while there was no centralized slide review in Patard's multicentric series.

Concordance between the original histologic classification and the histotype assigned after slide revision can be significantly affected by the year of treatment.[190] In our experience, a moderate concordance index was shown for the tumors diagnosed between 1984 and 1997, while we demonstrated an almost perfect concordance between original and reviewed histotype for the neoplasms observed after 1997. In our experience, after revision of the pathologic slides by a single experienced uropathologist, concordance with the initial diagnosis was 88.1% for conventional renal cell carcinomas treated before 1997 and 93% for those operated on

thereafter. Moreover, the most relevant data were that the concordance rate between initial diagnoses and those reported after revision in the papillary renal cell carcinoma subgroup increased from 71.4% in the 1984–97 period to 91% in the following period. Moreover, histologic subtype reassignment allowed a better prognostic stratification of the three most frequent histotypes. Patients with conventional renal cell carcinoma had a lower cancer-specific survival than those with papillary and chromophobe renal cell carcinoma, while no significant difference was reported between papillary and chromophobe renal cell carcinoma (Figure 1.82). Specifically, the subgroup of patients with locally advanced (pT3–4) or high-grade (G3–4) conventional renal cell carcinoma had lower cancer-specific survival probabilities, compared with those with papillary and chromophobe renal cell carcinoma.[190]

Presence of sarcomatoid features

The presence of sarcomatoid differentiation in renal cell carcinoma (Figure 1.83) is associated with a median survival of less than 1 year.[31,191] In cases of renal cell carcinoma with sarcomatoid features, de Peralta-Venturina et al reported 5- and 10-year survival rates of 22% and 13%, respectively. Although these authors reported an association between the amount of sarcomatoid differentiation and outcome in a univariate setting, this difference was not statistically significant after adjusting for stage.[31] Other authors have not identified a significant association, even in univariate analysis.[191,192]

The Mayo Clinic team reported cancer-specific survival rates at 2 years following surgery for patients with clear cell, papillary, and chromophobe renal cell carcinoma with sarcomatoid differentiation (Figure 1.84) of 30%, 40%, and 25%, respectively, compared with 84%, 96%, and 96%, respectively, for patients with clear cell, papillary, and chromophobe renal cell carcinoma without sarcomatoid differentiation.[173]
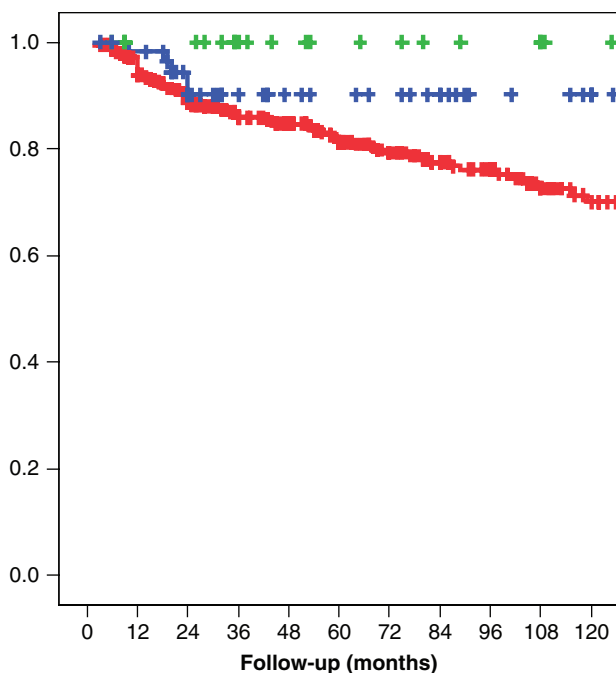
Figure 1.82
Cancer-specific survival according to the reviewed histologic subtypes (log-rank *p* value was 0.009). Patients with conventional RCC (red curve) had the worst cancer-related outcome, compared with the patients with papillary (blue curve; *p* = 0.03) or chromophobe RCC (green curve; *p* = 0.01). No statistically significant difference was observed between the prognosis of papillary and chromophobe RCC (*p* = 0.13).[190]
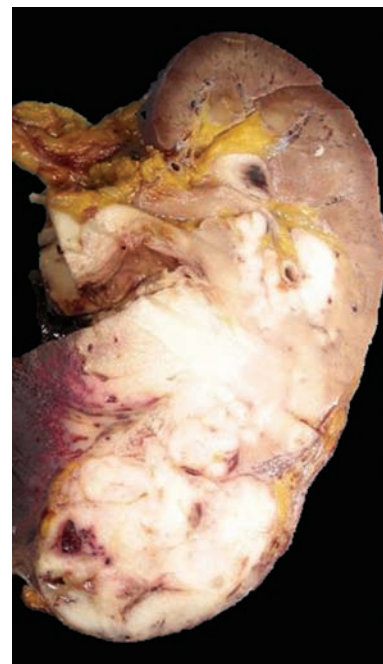
Figure 1.83
Clear cell renal cell carcinoma with sarcomatoid transformation: macroscopic appearance of a whitish-gray bulging tumor.
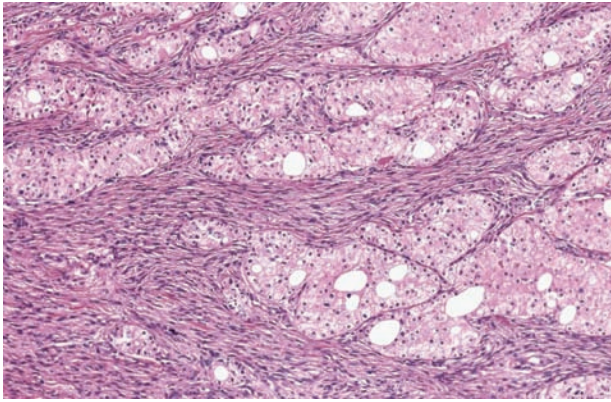
Figure 1.84
Sarcomatoid chromophobe renal cell carcinoma: admixture of sarcoma-like neoplastic areas with epithelial chromophobic neoplastic cells.
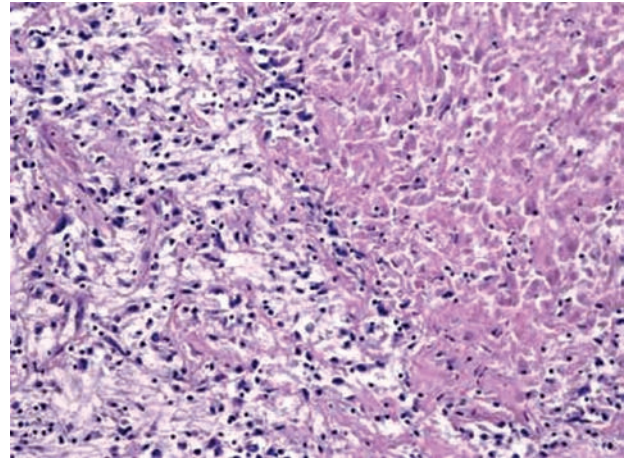
Figure 1.85
Clear cell renal cell carcinoma: necrosis.

Histologic tumor necrosis

The limited number of studies that have examined necrosis as a potential prognostic variable, the potential different impact of necrosis by histologic subtype, and the multiplicity of definitions of necrosis represented the main factors that explained the lack of recognition of tumor necrosis as a prognostic variable for renal cell carcinoma.[193]

The most common form of necrosis observed in renal cell carcinoma tumors is coagulative necrosis (Figure 1.85), characterized by homogeneous clusters and sheets of dead and degraded tumor cells that coalesce into an amorphous coagulum. This form of histologic coagulative necrosis produced an independent predictor of malignant progression and death from cancer in clear cell carcinoma.[160,179] However, the impact of histologic tumor necrosis on patient outcome varies by histologic subtype. Recently, Sengupta et al reported that although patients who have papillary renal cell carcinoma are more likely to have necrotic tumors compared with patients who have clear cell renal cell carcinoma or chromophobe renal cell carcinoma, the finding of necrosis in a papillary renal cell carcinoma is not associated significantly with death from disease. In contrast, the finding of histologic tumor necrosis in clear cell renal cell carcinoma or chromophobe renal cell carcinoma is indicative of aggressive tumor behavior.[193]

Ficarra et al demonstrated that histologic necrosis was present in 11% of patients with clear cell renal cell carcinoma.[183] The 5- and 10-year cancer-specific survival rates were 86% and 75%, respectively, in patients without coagulative necrosis, and 48% and 37% in patients with necrosis (log rank p value < 0.0001) (Figure 1.86). This histologic prognostic factor turned out significant at multivariate analysis.[194] However, the use of tumor necrosis as a prognostic factor remains controversial. Sorbellini et al found that the absence of tumor necrosis was associated with disease recurrence in patients with conventional renal cell carcinoma, although this association was not statistically significant on multivariate analysis.[194] Furthermore, the incidence of tumor necrosis was reported to be only 3% compared with 12% in the series reported by Ficarra et al[160] and 31% by Frank et al[179] in the cohort used to develop the Stage, Size, Grading and Necrosis (SSIGN) score.
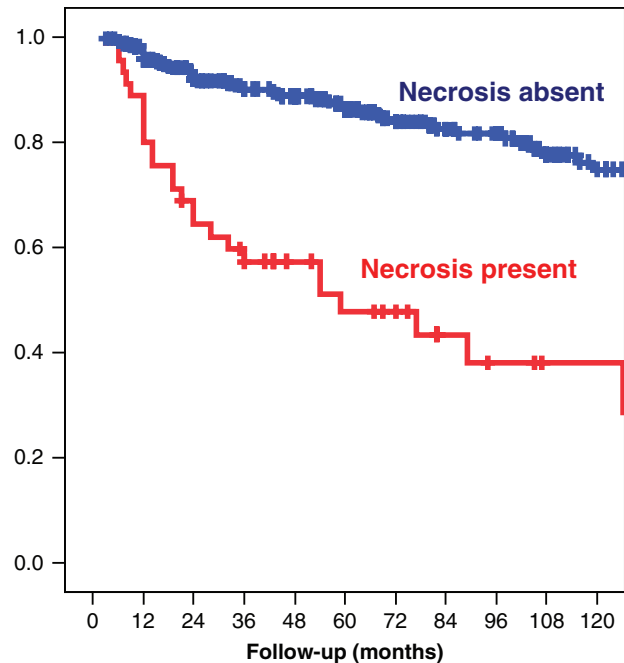
Figure 1.86
Cancer-specific survival probabilities according to presence of necrosis. Data extrapolated from 388 conventional RCC is treated at University of Verona (Cancer 103; 68: 2005).

Collecting system invasion

Urinary collecting system involvement is not included in the current TNM staging system. Tumors invading the urinary collecting system are usually symptomatic, with a higher stage and nuclear grade. It was reported that the presence of a collecting system invasion in high-stage tumors did not support a significantly worse prognosis, whereas in low-stage tumors this prognostic factor can negatively influence the cancer-specific survival rate.[195] Palapattu et al reported

that patients with collecting system invasion had a significantly lower 3-year cancer-specific survival rate than their counterparts who did not have involvement. In this study, multivariate analysis showed that collecting system invasion was an independent predictor of survival.[196]

In 2004, Terrone et al evaluated the pathologic reports of 671 patients who underwent radical nephrectomy for renal cell carcinoma. The 5-year cancer-specific survival rate was 45.5% in patients with urinary collecting system invasion and 64.7% in those without. Moreover, after stratification according to pathologic stage, the 5-year cancer-specific survival rate was significantly different only for the pT2 category. However, in this series urinary collecting system invasion did not result in an independent prognostic factor.[197]

Outcome predictive models have been developed with the intent to integrate known clinical and pathologic prognostic factors into a single system which might facilitate classification of patients into different prognostic categories. This system could be used to counsel patients, determine the need for adjuvant therapy, stratify patients for clinical trials, and develop appropriate postoperative surveillance programs that are tailored to a patient's risk for disease progression. The most important predictive models were developed in recent years by the Memorial Sloan-Kettering Cancer Center,[194,198] University of California – Los Angeles (UCLA),[199] and the Mayo Clinic.[179] All the models include histologic variables.

In 2001 Kattan et al proposed a nomogram to predict the 5-year probability of treatment failure in patients with newly diagnosed renal cell carcinoma. Their algorithm includes incidental, local, or systemic patient symptoms at presentation, histologic subtype, tumor size, and pathologic stage, and it resulted in a cancer specific survival index of 0.74.[198] However, since papillary and chromophobe tumors were not routinely assigned a nuclear grade, this feature was not included in their analysis despite the finding that nuclear grade provides important prognostic information in patients with clear cell renal cell carcinoma. To address this limitation Sorbellini et al recently presented a new prognostic nomogram focusing on the clear cell renal cell carcinoma variant that includes patient symptoms at presentation, tumor size, pathologic stage, Fuhrman nuclear grade, tumor necrosis, and microvascular invasion. The cancer specific survival index resulting from this nomogram was 0.82.[194]

In 2001, Zisman et al proposed a prognostic algorithm designed to predict overall survival in patients with and without metastatic renal cell carcinoma.[199] The UCLA Integrated Staging System (UISS) incorporates pathologic stage, ECOG performance status, and Fuhrman grade to classify patients into five prognostic categories, which are then used to predict overall survival 2 and 5 years following surgery. Subsequently, the same group proposed two simplified algorithms, one for N0M0 and one for N+ and/or M+ renal cell carcinoma, including only three risk groups.[200] The UISS predictive model was validated in patients with localized and metastatic tumors in two multicenter studies.[6,201]

In 2002, Frank et al introduced a further model to predict the prognosis of patients who have undergone radical nephrectomy for clear cell renal cell carcinoma.[179] Analyzing a cohort of 1800 patients treated at the Mayo Clinic from 1970 to 1998, the authors provided a multivariate analysis which indicated TNM stage, nuclear grade, tumor necrosis, and pathologic tumor size (>5 cm) as independent
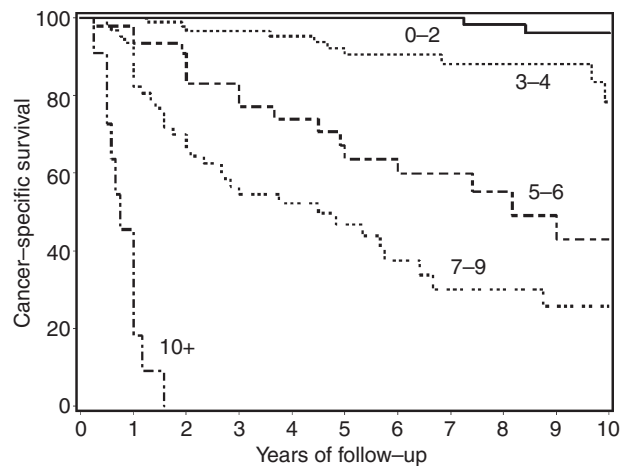
Figure 1.87

Estimated cancer-specific survival by the Mayo Clinic SSIGN score groupings in 388 patients with conventional RCC. In consideration of the limited number of patients in each SSIGN score category we sought to optimize patient stratification by collapsing the scores into fewer categories. Pairwise comparisons of outcome among adjacent scores suggested that patients could be stratified into 5 groups, that is SSIGN scores 0 to 2, 3 and 4, 5 and 6, 7 to 9, and 10 or greater.[202a]

predictive variables of cancer-specific survival. These variables were included into an algorithm, where each variable was scored according to the risk ratio of the bootstrap analysis. It resulted in the Stage, Size, Grade, and Necrosis (SSIGN) score used to estimate 1-, 3-, 5-, 7- and 10-year cancer-specific survival. The score is calculated as +1 (pT2), +2 (pT3a, pT3b, pT3c), +2 (pN1, pN2), +4 (M1), +2 (tumor size 5 cm or more), +1 (grade 3), +3 (grade 4), +2 (necrosis), and 0 otherwise.

The application of this prognostic algorithm to a series of 388 patients with conventional renal cell carcinoma proved to be particularly useful to predict outcome (Figure 1.87).[202] For example, patients with favorable SSIGN scores of 0 to 2 and 3 or 4 had 5-year cancer-specific survival rates of 100% and 91%, respectively. In contrast, patients with moderate and high scores of 5 or 6 and 7 to 9 had 5-year cancer-specific survival rates of 64% and 47%, respectively. All patients with a score of 10 or more died of disease within 2 years of surgery. In addition, all pathologic features in the SSIGN score algorithm except tumor size were significantly associated with patient outcome in a multivariate setting. Lastly, the cancer specific survival index or measure of predictive ability of the SSIGN score was 0.88, which was considerably higher than that achieved using any single feature.[203–212]

The SSIGN score has limitations. First, the SSIGN score only applies to patients who have clear cell renal cell carcinoma. However, the Mayo Clinic team believes that it is inappropriate to use a single prognostic algorithm for all histologic subtypes. Second, the SSIGN score could be improved by incorporating recent changes to the TNM classification, including the pT1a and pT1b subclassifications, the stratification of high-stage tumors by fat invasion and tumor thrombus level, and the assessment of extranodal extension.[173]

Part 6

Pediatric tumors

Nephroblastoma (Wilms' tumor) comprises more than 85% of pediatric renal tumors and 5% of childhood cancers. It is usually found in children 2 to 4 years old; it is relatively uncommon in the first six months of life and in children older than 6 years, whereas it is rare in the neonatal period. The male to female ratio is 1:1. Five percent of the tumors are multicentric and bilateral. The associations with cryptorchidism, hypospadias, other genital anomalies, hemihypertrophy, and aniridia are well recognized and described in different genetic syndromes such as the Beckwith–Wiedemann, Wilms–aniridia–genital anomaly–retardation, and Denys–Drash syndromes due to different genetic alterations. Nephroblastoma rarely occurs in adults.

Grossly it presents as a mass, usually larger than 5 cm, with a solid, soft, and grayish or pinkish appearance, resembling brain tissue (Figure 1.88). Hemorrhage and necrosis are frequently present. The tumor is usually surrounded by a prominent pseudocapsule composed of compressed renal and perirenal tissues. Cystic tumors macroscopically indistinguishable from cystic nephromas, which present small foci of blastema, immature appearing stromal cells and primitive epithelium, are classified as cystic, partially differentiated nephroblastomas.

Microscopically, nephroblastoma is typically triphasic, being composed of variable admixtures of blastema, epithelium, and stroma (Figure 1.89). However, in some neoplasms only two, and occasionally only one, components are present. The blastemal component can grow in three different patterns: nodular, serpentine, and diffuse. The blastemal cells are small, densely packed, and show oval to elongated nuclei with numerous mitoses. The epithelial component usually consists of small tubules lined by primitive columnar cells and abortive glomeruli. The stromal component can differentiate along the lines of almost any type of soft tissue: loose myxoid, fibroblastic spindle cell stroma, and skeletal muscle are the most common.

Nephroblastomas are divided into two categories: favorable and unfavorable histologies, based on the absence or presence of anaplasia. Anaplasia has been defined as the combination of cells with very large hyperchromatic nuclei and multipolar mitotic figures. Anaplasia is found in approximately 6% of Wilms' tumors; it is rare in patients younger than 1 year and more than 80% of patients are older than 2. Even small foci of anaplasia can be associated with an adverse outcome. Thus, it is important to sample Wilms' tumor specimens extensively. Some Wilms' tumors have a monomorphous epithelial appearance and can pose difficult diagnostic problems in their distinction from renal cell carcinoma.[203,209,212,213]

Mesoblastic nephroma is the most common kidney tumor in the first 3 months of life, and is uncommon after 6 months. It comprises 5% of pediatric renal neoplasms. Mesoblastic nephroma is benign but it has infiltrative borders which must be studied carefully because the risk of recurrence appears to be dependent upon the completeness of the resection.

Grossly this neoplasm is usually large and its cut surface resembles that of a leiomyoma (Figure 1.90): firm, whorled or trabeculated, and light colored. The tumor is not encapsulated and typically interdigitates with the surrounding renal parenchyma. Histologically it is a moderately cellular proliferation of thick interlacing bundles of spindle cells with elongate nuclei which usually infiltrate

Figure 1.89
Wilms' tumor: nephroblastoma is typically triphasic, being composed of variable admixtures of blastema, epithelium, and stroma.
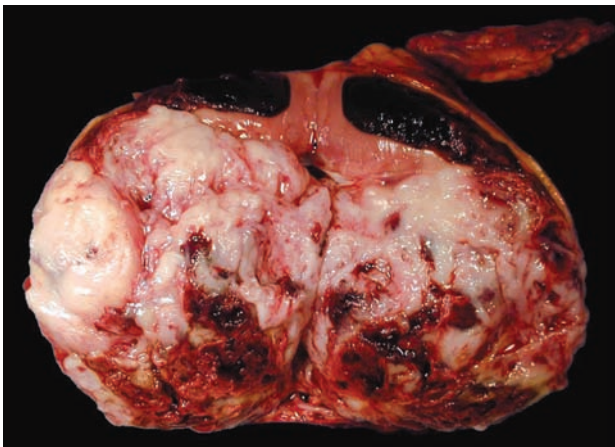
Figure 1.88
Wilms' tumor: large tumor resembling a cerebral mass.
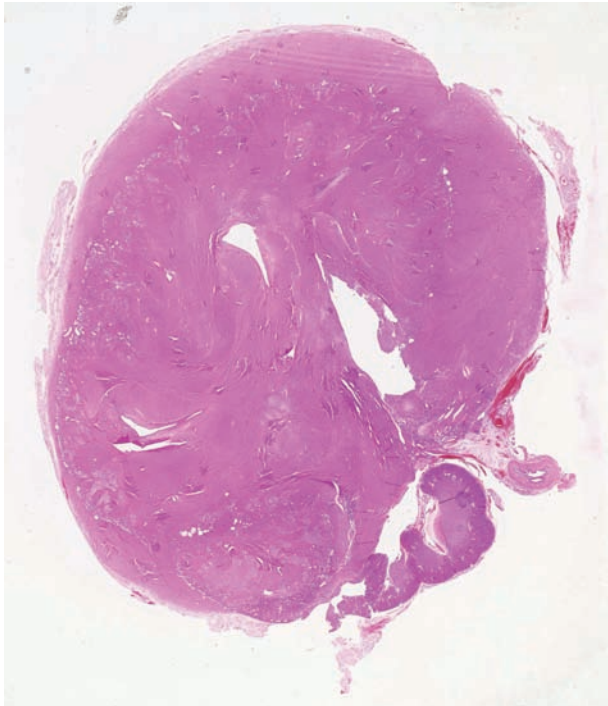
Figure 1.90
Mesoblastic nephroma: grossly this neoplasm is usually large and its cut surface resembles that of a leiomyoma.
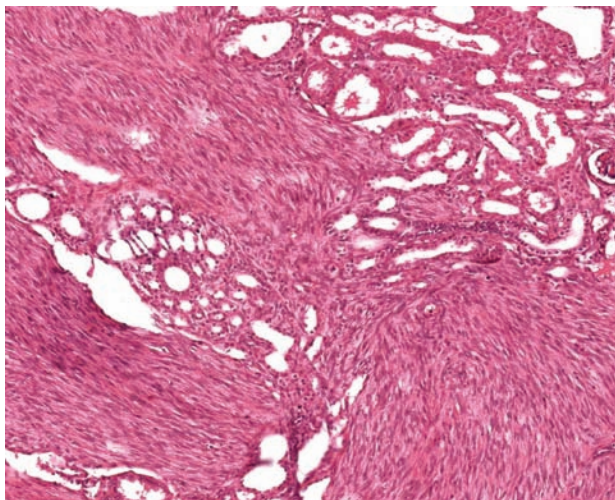
Figure 1.91
Mesoblastic nephroma: it is a moderately cellular proliferation of thick interlacing bundles of spindle cells with elongated nuclei which usually infiltrate renal and perirenal tissues, resembling a fibromatosis or a leiomyoma. Glomeruli and renal tubules are commonly entrapped.

renal and perirenal tissues resembling a fibromatosis or a leiomyoma (Figure 1.91). Glomeruli and renal tubules are commonly entrapped. Mitotic figures are usually rare. Another pattern consists of a densely cellular proliferation of polygonal cells with more frequent mitotic figures (8–30 per 10 high-power fields). These tumors are called 'cellular mesoblastic nephromas'.[214,215]

Clear cell sarcoma of the kidney (so-called bone-metastasizing renal tumor of childhood) comprises 4% of pediatric renal tumors; its male to female ratio is 1.6:1. It occurs usually at 2–3 years of age and it is extremely rare before 6 months. This tumor is highly aggressive with a high mortality rate. Grossly clear cell sarcoma presents as a well-circumscribed, firm, gray mass. Histologically, it displays a variable pattern of growth (epithelioid, spindle, sclerosing, myxoid, palisanding) and it is composed of monomorphic, small, round or spindle or epithelioid cells intermingled with a prominent network of vascular septa.[216]

Rhabdoid tumor of the kidney comprises 2% of pediatric renal neoplasms. Its male to female ratio is 1.5:1. Ninety percent of the cases occur in patients before 3 years of age. The patients frequently die within 1 year of diagnosis. It is an infiltrative, necrotic hemorrhagic tumor composed of sheets of large discohesive polygonal cells with large vesicular nuclei showing a prominent central nucleolus.[217,218]

A fifth pediatric kidney tumor is called *ossifying tumor* and is extremely rare.[219]

References

1. Cohen HT, McGovern FJ. Renal cell carcinoma. N Engl J Med 2005; 353(23): 2477–90.
2. Chow WH, McLaughlin JK, Mandel JS et al. Obesity and risk of renal cell cancer. Cancer Epidemiol Biomarkers Prev 1996; 5(1): 17–21.
3. Wolk A, Lindblad P, Adami HO. Nutrition and renal cell cancer. Cancer Causes Control 1996; 7(1): 5–18.
4. Eble JN SG, Epstein J, Sesterhenn I. WHO 2004: Pathology and Genetics of Tumors of the Urinary System and Male Genital Organs. Lyon, France: IARC, 2004.
5. Ficarra V, Prayer-Galetti T, Novella G et al. Incidental detection beyond pathological factors as prognostic predictor of renal cell carcinoma. Eur Urol 2003; 43(6): 663–9.
6. Patard JJ, Leray E, Cindolo L et al. Multi-institutional validation of a symptom based classification for renal cell carcinoma. J Urol 2004; 172(3): 858–62.
7. Bosniak MA. Problems in the radiologic diagnosis of renal parenchymal tumors. Urol Clin North Am 1993; 20(2): 217–30.
8. Bosniak MA. Renal cell carcinoma. N Engl J Med 1997; 336(11): 810–11.
9. Hilton S. Imaging of renal cell carcinoma. Semin Oncol 2000; 27(2): 150–9.
10. Ritchie AW, Chisholm GD. The natural history of renal carcinoma. Semin Oncol 1983; 10(4): 390–400.
11. Mevorach RA, Segal AJ, Tersegno ME et al. Renal cell carcinoma: incidental diagnosis and natural history: review of 235 cases. Urology 1992; 39(6): 519–22.
12. Russo P. Renal cell carcinoma: presentation, staging, and surgical treatment. Semin Oncol 2000; 27(2): 160–76.
13. Cronin RE. Renal cell carcinoma. Am J Med Sci 1991; 302(4): 249–59.
14. Rathmell WK, Godley PA. Renal cell carcinoma. Curr Opin Oncol 2004; 16(3): 247–52.
15. Bjorge T, Tretli S, Engeland A. Relation of height and body mass index to renal cell carcinoma in two million Norwegian men and women. Am J Epidemiol 2004; 160(12): 1168–76.
16. McClennan BL. Oncologic imaging. Staging and follow-up of renal and adrenal carcinoma. Cancer 1991; 67(4 Suppl): 1199–208.
17. Eble JN, Sauter G, Epstein JI et al. WHO: Tumors of the Urinary System and Male Genital Organs. Lyon, France: IARC Press, 2004.
18. Kovacs G, Akhtar M, Beckwith BJ et al. The Heidelberg classification of renal cell tumors. J Pathol 1997; 183(2): 131–3.
19. Storkel S, Eble JN, Adlakha K et al. Classification of renal cell carcinoma: Workgroup No. 1. Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC). Cancer 1997; 80(5): 987–9.

20. Staehler M, Rohrmann K, Haseke N et al. Targeted agents for the treatment of advanced renal cell carcinoma. Curr Drug Targets 2005; 6(7): 835–46.

21. Grignon DJ, Che M. Clear cell renal cell carcinoma. Clin Lab Med 2005; 25(2): 305–16.

22. Eble JN, Bonsib SM. Extensively cystic renal neoplasms: cystic nephroma, cystic partially differentiated nephroblastoma, multilocular cystic renal cell carcinoma, and cystic hamartoma of renal pelvis. Semin Diagn Pathol 1998; 15(1): 2–20.

23. Murad T, Komaiko W, Oyasu R et al. Multilocular cystic renal carcinoma. Am J Clin Pathol 1991; 95(5): 633–7.

24. Amin MB, Corless CL, Renshaw AA et al. Papillary (chromophil) renal cell carcinoma: histomorphologic characteristics and evaluation of conventional pathologic prognostic parameters in 62 cases. Am J Surg Pathol 1997; 21(6): 621–35.

25. Delahunt B, Velickovic M, Grebe SK. Evolving classification of renal cell neoplasia. Expert Rev Anticancer Ther 2001; 1(4): 576–84.

26. Allory Y, Ouazana D, Boucher E et al. Papillary renal cell carcinoma. Prognostic value of morphological subtypes in a clinicopathologic study of 43 cases. Virch Arch 2003; 442(4): 336–42.

27. Delahunt B, Eble JN. Papillary renal cell carcinoma: a clinicopathologic and immunohistochemical study of 105 tumors. Mod Pathol 1997; 10(6): 537–44.

28. Delahunt B, Eble JN, McCredie MR et al. Morphologic typing of papillary renal cell carcinoma: comparison of growth kinetics and patient survival in 66 cases. Hum Pathol 2001; 32(6): 590–5.

29. Hes O, Brunelli M, Michal M et al. Oncocytic papillary renal cell carcinoma: a clinicopathologic, immunohistochemical, ultrastructural, and interphase cytogenetic study of 12 cases. Ann Diagn Pathol 2006; 10(3): 133–9.

30. Delahunt B. Sarcomatoid renal carcinoma: the final common dedifferentiation pathway of renal epithelial malignancies. Pathology 1999; 31(3): 185–90.

31. de Peralta-Venturina M, Moch H, Amin M et al. Sarcomatoid differentiation in renal cell carcinoma: a study of 101 cases. Am J Surg Pathol 2001; 25(3): 275–84.

32. Crotty TB, Farrow GM, Lieber MM. Chromophobe cell renal carcinoma: clinicopathological features of 50 cases. J Urol 1995; 154(3): 964–7.

33. Hes O, Vanecek T, Perez-Montiel DM et al. Chromophobe renal cell carcinoma with microcystic and adenomatous arrangement and pigmentation–a diagnostic pitfall. Morphological, immunohistochemical, ultrastructural and molecular genetic report of 20 cases. Virch Arch 2005; 446(4): 383–93.

34. Thoenes W, Storkel S, Rumpelt HJ et al. Chromophobe cell renal carcinoma and its variants–a report on 32 cases. J Pathol 1988; 155(4): 277–87.

35. Thoenes W, Storkel S, Rumpelt HJ. Human chromophobe cell renal carcinoma. Virch Arch B Cell Pathol Incl Mol Pathol 1985; 48(3): 207–17.

36. Peyromaure M, Misrai V, Thiounn N et al. Chromophobe renal cell carcinoma: analysis of 61 cases. Cancer 2004; 100(7): 1406–10.

37. Kawada Y, Nakamura M, Ishida E et al. Aberrations of the p14(ARF) and p16(INK4a) genes in renal cell carcinomas. Jpn J Cancer Res 2001; 92(12): 1293–9.

38. Martignoni G, Eble JN, Brunelli M et al. Chromophobe renal cell carcinoma: a clinicopathologic study of 100 cases. Mod Pathol 2003; 16: 161A.

39. Akhtar M, Kardar H, Linjawi T et al. Chromophobe cell carcinoma of the kidney. A clinicopathologic study of 21 cases. Am J Surg Pathol 1995; 19(11): 1245–56.

40. Latham B, Dickersin GR, Oliva E. Subtypes of chromophobe cell renal carcinoma: an ultrastructural and histochemical study of 13 cases. Am J Surg Pathol 1999; 23(5): 530–5.

41. Tickoo SK, Lee MW, Eble JN et al. Ultrastructural observations on mitochondria and microvesicles in renal oncocytoma, chromophobe renal cell carcinoma, and eosinophilic variant of conventional (clear cell) renal cell carcinoma. Am J Surg Pathol 2000; 24(9): 1247–56.

42. Martignoni G, Eble JN, Brunelli M et al. Chromophobe renal cell carcinoma: a clinico-pathologic study of 100 cases. Mod Pathol 2003; 1: 161A.

43. Tickoo SK, Amin MB, Zarbo RJ. Colloidal iron staining in renal epithelial neoplasms, including chromophobe renal cell carcinoma: emphasis on technique and patterns of staining. Am J Surg Pathol 1998; 22(4): 419–24.

44. Cossu-Rocca P, Eble JN, Zhang S et al. Acquired cystic disease-associated renal tumors: an immunohistochemical and fluorescence in situ hybridization study. Mod Pathol 2006; 19(6): 780–7.

45. Fleming S, Lewi HJ. Collecting duct carcinoma of the kidney. Histopathology 1986; 10(11): 1131–41.

46. Davis CJ Jr, Mostofi FK, Sesterhenn IA. Renal medullary carcinoma. The seventh sickle cell nephropathy. Am J Surg Pathol 1995; 19(1): 1–11.

47. Srigley JR, Eble JN. Collecting duct carcinoma of kidney. Semin Diagn Pathol 1998; 15(1): 54–67.

48. Fuzesi L, Cober M, Mittermayer C. Collecting duct carcinoma: cytogenetic characterization. Histopathology 1992; 21(2): 155–60.

49. Eble JN, Hull MT. Morphologic features of renal oncocytoma: a light and electron microscopic study. Hum Pathol 1984; 15(11): 1054–61.

50. Tickoo SK, dePeralta-Venturina MN, Harik LR et al. Spectrum of epithelial neoplasms in end-stage renal disease: an experience from 66 tumor-bearing kidneys with emphasis on histologic patterns distinct from those in sporadic adult renal neoplasia. Am J Surg Pathol 2006; 30(2): 141–53.

51. Perez-Ordonez B, Hamed G, Campbell S et al. Renal oncocytoma: a clinicopathologic study of 70 cases. Am J Surg Pathol 1997; 21(8): 871–83.

52. Amin MB, Crotty TB, Tickoo SK et al. Renal oncocytoma: a reappraisal of morphologic features with clinicopathologic findings in 80 cases. Am J Surg Pathol 1997; 21(1): 1–12.

53. Cochand-Priollet B, Molinie V, Bougaran J et al. Renal chromophobe cell carcinoma and oncocytoma. A comparative morphologic, histochemical, and immunohistochemical study of 124 cases. Arch Pathol Lab Med 1997; 121(10): 1081–6.

54. Skinnider BF, Jones EC. Renal oncocytoma and chromophobe renal cell carcinoma. A comparison of colloidal iron staining and electron microscopy. Am J Clin Pathol 1999; 111(6): 796–803.

55. Muir TE, Cheville JC, Lager DJ. Metanephric adenoma, nephrogenic rests, and Wilms' tumor: a histologic and immunophenotypic comparison. Am J Surg Pathol 2001; 25(10): 1290–6.

56. Grignon DJ, Eble JN. Papillary and metanephric adenomas of the kidney. Semin Diagn Pathol 1998; 15(1): 41–53.

57. Davis CJ Jr, Barton JH, Sesterhenn IA et al. Metanephric adenoma. Clinicopathological study of fifty patients. Am J Surg Pathol 1995; 19(10): 1101–14.

58. Bonetti F, Pea M, Martignoni G et al. Clear cell ('sugar') tumor of the lung is a lesion strictly related to angiomyolipoma–the concept of a family of lesions characterized by the presence of the perivascular epithelioid cells (PEC). Pathology 1994; 26(3): 230–6.

59. Martignoni G, Pea M, Rocca PC et al. Renal pathology in the tuberous sclerosis complex. Pathology 2003; 35(6): 505–12.

60. Tallarigo C, Baldassarre R, Bianchi G et al. Diagnostic and therapeutic problems in multicentric renal angiomyolipoma. J Urol 1992; 148(6): 1880–4.

61. Martignoni G, Pea M, Rigaud G et al. Renal angiomyolipoma with epithelioid sarcomatous transformation and metastases: demonstration of the same genetic defects in the primary and metastatic lesions. Am J Surg Pathol 2000; 24(6): 889–94.

62. Carbonara C, Longa L, Grosso E et al. Apparent preferential loss of heterozygosity at TSC2 over TSC1 chromosomal region in tuberous sclerosis hamartomas. Genes Chromosomes Cancer 1996; 15(1): 18–25.

63. Kilicaslan I, Gulluoglu MG, Dogan O et al. Intraglomerular microlesions in renal angiomyolipoma. Hum Pathol 2000; 31(10): 1325–8.

64. Martignoni G, Bonetti F, Pea M et al. Renal disease in adults with TSC2/PKD1 contiguous gene syndrome. Am J Surg Pathol 2002; 26(2): 198–205.

65. Eble JN, Amin MB, Young RH. Epithelioid angiomyolipoma of the kidney: a report of five cases with a prominent and diagnostically confusing epithelioid smooth muscle component. Am J Surg Pathol 1997; 21(10): 1123–30.

66. Martignoni G, Pea M, Bonetti F et al. Carcinomalike monotypic epithelioid angiomyolipoma in patients without evidence of tuberous sclerosis: a clinicopathologic and genetic study. Am J Surg Pathol 1998; 22(6): 663–72.

67. Pea M, Bonetti F, Martignoni G et al. Apparent renal cell carcinomas in tuberous sclerosis are heterogeneous: the identification of malignant epithelioid angiomyolipoma. Am J Surg Pathol 1998; 22(2): 180–7.

68. Pan CC, Jong YJ, Chai CY et al. Comparative genomic hybridization study of perivascular epithelioid cell tumor: molecular genetic evidence of perivascular epithelioid cell tumor as a distinctive neoplasm. Hum Pathol 2006; 37(5): 606–12.

69. Martignoni G, Pea M, Bonetti F et al. Oncocytoma-like angiomyolipoma. A clinicopathologic and immunohistochemical study of 2 cases. Arch Pathol Lab Med 2002; 126(5): 610–12.

70. Davis CJ, Barton JH, Sesterhenn IA. Cystic angiomyolipoma of the kidney: a clinicopathologic description of 11 cases. Mod Pathol 2006; 19(5): 669–74.

71. Fine SW, Reuter VE, Epstein JI et al. Angiomyolipoma with epithelial cysts (AMLEC): a distinct cystic variant of angiomyolipoma. Am J Surg Pathol 2006; 30(5): 593–9.

72. Argani P, Antonescu CR, Illei PB et al. Primary renal neoplasms with the ASPL-TFE3 gene fusion of alveolar soft part sarcoma: a distinctive tumor entity previously included among renal cell carcinomas of children and adolescents. Am J Pathol 2001; 159(1): 179–92.

73. Argani P, Antonescu CR, Couturier J et al. PRCC-TFE3 renal carcinomas: morphologic, immunohistochemical, ultrastructural, and molecular analysis of an entity associated with the t(X;1)(p11.2;q21). Am J Surg Pathol 2002; 26(12): 1553–66.

74. Argani P, Lal P, Hutchinson B et al. Aberrant nuclear immunoreactivity for TFE3 in neoplasms with TFE3 gene fusions: a sensitive and specific immunohistochemical assay. Am J Surg Pathol 2003; 27(6): 750–61.

75. Argani P, Lui MY, Couturier J et al. A novel CLTC-TFE3 gene fusion in pediatric renal adenocarcinoma with t(X;17)(p11.2;q23). Oncogene 2003; 22(34): 5374–8.

76. Argani P, Hawkins A, Griffin CA et al. A distinctive pediatric renal neoplasm characterized by epithelioid morphology, basement membrane production, focal HMB45 immunoreactivity, and t(6;11)(p21.1;q12) chromosome translocation. Am J Pathol 2001; 158(6): 2089–96.

77. Argani P, Lae M, Hutchinson B et al. Renal carcinomas with the t(6;11)(p21;q12): clinicopathologic features and demonstration of the specific alpha-TFEB gene fusion by immunohistochemistry, RT-PCR, and DNA PCR. Am J Surg Pathol 2005; 29(2): 230–40.

78. Eble JN. Mucinous tubular and spindle cell carcinoma and post-neuroblastoma carcinoma: newly recognised entities in the renal cell carcinoma family. Pathology 2003; 35(6): 499–504.

79. Medeiros LJ, Palmedo G, Krigman HR et al. Oncocytoid renal cell carcinoma after neuroblastoma: a report of four cases of a distinct clinicopathologic entity. Am J Surg Pathol 1999; 23(7): 772–80.

80. Rakozy C, Schmahl GE, Bogner S et al. Low-grade tubular-mucinous renal neoplasms: morphologic, immunohistochemical, and genetic features. Mod Pathol 2002; 15(11): 1162–71.

81. Ferlicot S, Allory Y, Comperat E et al. Mucinous tubular and spindle cell carcinoma: a report of 15 cases and a review of the literature. Virch Arch 2005; 447(6): 978–83.

82. Kuroda N, Toi M, Hiroi M et al. Review of mucinous tubular and spindle-cell carcinoma of the kidney with a focus on clinical and pathobiological aspects. Histol Histopathol 2005; 20(1): 221–4.

83. Hes O, Hora M, Perez-Montiel DM et al. Spindle and cuboidal renal cell carcinoma, a tumor having frequent association with nephrolithiasis: report of 11 cases including a case with hybrid conventional renal cell carcinoma/spindle and cuboidal renal cell carcinoma components. Histopathology 2002; 41(6): 549–55.

84. Mukhopadhyay D, Datta K. Multiple regulatory pathways of vascular permeability factor/vascular endothelial growth factor (VPF/VEGF) expression in tumors. Semin Cancer Biol 2004; 14(2): 123–30.

85. Adsay NV, Eble JN, Srigley JR et al. Mixed epithelial and stromal tumor of the kidney. Am J Surg Pathol 2000; 24(7): 958–70.

86. Michal M, Hes O, Bisceglia M et al. Mixed epithelial and stromal tumors of the kidney. A report of 22 cases. Virch Arch 2004; 445(4): 359–67.

87. Shurtleff BT, Shvarts O, Rajfer J. Carcinoid tumor of the kidney: case report and review of the literature. Rev Urol 2005; 7(4): 229–33.

88. van den Berg E, Gouw AS, Oosterhuis JW et al. Carcinoid in a horseshoe kidney. Morphology, immunohistochemistry, and cytogenetics. Cancer Genet Cytogenet 1995; 84(2): 95–8.

89. Begin LR, Guy L, Jacobson SA et al. Renal carcinoid and horseshoe kidney: a frequent association of two rare entities–a case report and review of the literature. J Surg Oncol 1998; 68(2): 113–19.

90. Porcaro AB, D'Amico A, Novella G et al. Primary lymphoma of the kidney. Report of a case and update of the literature. Arch Ital Urol Androl 2002; 74(1): 44–7.

91. Sneige N, Dekmezian RH, Silva EG et al. Pseudoparasitic Liesegang structures in perirenal hemorrhagic cysts. Am J Clin Pathol 1988; 89(2): 148–53.

92. Vizcaino JR, Macedo-Dias JA, Teixeira-de-Sousa JM et al. Pseudotumor of renal pelvis: Liesegang rings mimicking a solid neoplasm of the renal pelvis. Histopathology 2005; 47(1): 115–17.

93. Lew S, Siegal A, Aronheim M. Renal cell carcinoma with malakoplakia. Eur Urol 1988; 14(5): 426–8.

94. Costello CB, Jasani B, Kumar S. Tamm–Horsfall protein in human renal tumors. Anticancer Res 1991; 11(6): 2159–61.

95. Howie AJ, Smithson N, Raafat F. Distinctive patterns of renal neoplasms containing Tamm–Horsfall protein. Virch Arch A Pathol Anat Histopathol 1993; 422(5): 361–5.

96. Velickovic M, Delahunt B, Storkel et al. VHL and FHIT locus loss of heterozygosity is common in all renal cancer morphotypes but differs in pattern and prognostic significance. Cancer Res 2001; 61(12): 4815–19.

97. Carroll PR, Murty VV, Reuter V et al. Abnormalities at chromosome region 3p12–14 characterize clear cell renal carcinoma. Cancer Genet Cytogenet 1987; 26(2): 253–9.

98. Ogawa O, Kakehi Y, Ogawa K et al. Allelic loss at chromosome 3p characterizes clear cell phenotype of renal cell carcinoma. Cancer Res 1991; 51(3): 949–53.

99. Kovacs G. Molecular differential pathology of renal cell tumors. Histopathology 1993; 22(1): 1–8.

100. van der Hout AH, van den Berg E, van der Vlies P et al. Loss of heterozygosity at the short arm of chromosome 3 in renal cell cancer correlates with the cytological tumor type. Int J Cancer 1993; 53(3): 353–7.

101. Zbar B. Von Hippel-Lindau disease and sporadic renal cell carcinoma. Cancer Surv 1995; 25: 219–32.

102. Clifford SC, Maher ER. Von Hippel–Lindau disease: clinical and molecular perspectives. Adv Cancer Res 2001; 82: 85–105.

103. Kaelin WG Jr. The von Hippel–Lindau tumor suppressor gene and kidney cancer. Clin Cancer Res 2004; 10(18 Pt 2): 6290S-5S.

104. Linehan WM, Walther MM, Zbar B. The genetic basis of cancer of the kidney. J Urol 2003; 170(6 Pt 1): 2163–72.

105. Corless CL, Aburatani H, Fletcher JA et al. Papillary renal cell carcinoma: quantitation of chromosomes 7 and 17 by FISH, analysis of chromosome 3p for LOH, and DNA ploidy. Diagn Mol Pathol 1996; 5(1): 53–64.

106. Brunelli M, Eble JN, Zhang S et al. Gains of chromosomes 7, 17, 12, 16, and 20 and loss of Y occur early in the evolution of papillary renal cell neoplasia: a fluorescent in situ hybridization study. Mod Pathol 2003; 16(10): 1053–9.

107. Jones TD, Eble JN, Wang M et al. Molecular genetic evidence for the independent origin of multifocal papillary tumors in patients with papillary renal cell carcinomas. Clin Cancer Res 2005; 11(20): 7226–33.

108. Jiang F, Richter J, Schraml P et al. Chromosomal imbalances in papillary renal cell carcinoma: genetic differences between histological subtypes. Am J Pathol 1998; 153(5): 1467–73.

109. Sanders ME, Mick R, Tomaszewski JE et al. Unique patterns of allelic imbalance distinguish type 1 from type 2 sporadic papillary renal cell carcinoma. Am J Pathol 2002; 161(3): 997–1005.

110. Zhuang Z, Park WS, Pack S et al. Trisomy 7-harbouring non-random duplication of the mutant MET allele in hereditary papillary renal carcinomas. Nat Genet 1998; 20(1): 66–9.

111. Schmidt L, Duh FM, Chen F et al. Germline and somatic mutations in the tyrosine kinase domain of the MET proto-oncogene in papillary renal carcinomas. Nat Genet 1997; 16(1): 68–73.

112. Stewart L, Glenn G, Toro JR. Cutaneous leiomyomas: a clinical marker of risk for hereditary leiomyomatosis and renal cell cancer. Dermatol Nurs 2006; 18(4): 335–41; quiz 42.

113. Alam NA, Olpin S, Rowan A et al. Missense mutations in fumarate hydratase in multiple cutaneous and uterine leiomyomatosis and renal cell cancer. J Mol Diagn 2005; 7(4): 437–43.

114. Chan I, Wong T, Martinez-Mir A et al. Familial multiple cutaneous and uterine leiomyomas associated with papillary renal cell cancer. Clin Exp Dermatol 2005; 30(1): 75–8.

115. Speicher MR, Schoell B, du Manoir S et al. Specific loss of chromosomes 1, 2, 6, 10, 13, 17, and 21 in chromophobe renal cell carcinomas revealed by comparative genomic hybridization. Am J Pathol 1994; 145(2): 356–64.

116. Schwerdtle RF, Storkel S, Neuhaus C et al. Allelic losses at chromosomes 1p, 2p, 6p, 10p, 13q, 17p, and 21q significantly correlate with the chromophobe subtype of renal cell carcinoma. Cancer Res 1996; 56(13): 2927–30.

117. Kovacs A, Kovacs G. Low chromosome number in chromophobe renal cell carcinomas. Genes Chromosomes Cancer 1992; 4(3): 267–8.

118. Bugert P, Gaul C, Weber K et al. Specific genetic changes of diagnostic importance in chromophobe renal cell carcinomas. Lab Invest 1997; 76(2): 203–8.

119. Brunelli M, Eble JN, Zhang S et al. Eosinophilic and classic chromophobe renal cell carcinomas have similar frequent losses of multiple chromosomes from among chromosomes 1, 2, 6, 10, and 17, and this pattern of genetic abnormality is not present in renal oncocytoma. Mod Pathol 2005; 18(2): 161–9.

120. Birt AR, Hogg GR, Dube WJ et al. Hereditary multiple fibrofolliculomas with trichodiscomas and acrochordons. Arch Dermatol 1977; 113(12): 1674–7.

121. Pavlovich CP, Walther MM, Eyler RA et al. Renal tumors in the Birt–Hogg–Dube syndrome. Am J Surg Pathol 2002; 26(12): 1542–52.

122. Tickoo SK, Reuter VE, Amin MB et al. Renal oncocytosis: a morphologic study of fourteen cases. Am J Surg Pathol 1999; 23(9): 1094–101.

123. Khoo SK, Kahnoski K, Sugimura J et al. Inactivation of BHD in sporadic renal tumors. Cancer Res 2003; 63(15): 4583–7.

124. Warren MB, Torres-Cabala CA, Turner ML et al. Expression of Birt–Hogg–Dube gene mRNA in normal and neoplastic human tissues. Mod Pathol 2004; 17(8): 998–1011.

125. Al-Saleem T, Cairns P, Dulaimi EA et al. The genetics of renal oncocytosis: a possible model for neoplastic progression. Cancer Genet Cytogenet 2004; 152(1): 23–8.

126. Antonelli A, Portesi E, Cozzoli A et al. The collecting duct carcinoma of the kidney: a cytogenetical study. Eur Urol 2003; 43(6): 680–5.

127. Schwerdtle RF, Winterpacht A, Storkel S et al. Loss of heterozygosity studies and deletion mapping identify two putative chromosome 14q tumor suppressor loci in renal oncocytomas. Cancer Res 1997; 57(22): 5009–12.

128. Lindgren V, Paner GP, Omeroglu A et al. Cytogenetic analysis of a series of 13 renal oncocytomas. J Urol 2004; 171(2 Pt 1): 602–4.

129. Crotty TB, Lawrence KM, Moertel CA et al. Cytogenetic analysis of six renal oncocytomas and a chromophobe cell renal carcinoma. Evidence that −Y, −1 may be a characteristic anomaly in renal oncocytomas. Cancer Genet Cytogenet 1992; 61(1): 61–6.

130. Presti JC Jr, Moch H, Reuter VE et al. Comparative genomic hybridization for genetic analysis of renal oncocytomas. Genes Chromosomes Cancer 1996; 17(4): 199–204.

131. Warfel KA, Eble JN. Renal oncocytomatosis. J Urol 1982; 127(6): 1179–80.

132. Brunelli M, Eble JN, Zhang S et al. Metanephric adenoma lacks the gains of chromosomes 7 and 17 and loss of Y that are typical of papillary renal cell carcinoma and papillary adenoma. Mod Pathol 2003; 16(10): 1060–3.

133. Henske EP, Neumann HP, Scheithauer BW et al. Loss of heterozygosity in the tuberous sclerosis (TSC2) region of chromosome band 16p13 occurs in sporadic as well as TSC-associated renal angiomyolipomas. Genes Chromosomes Cancer 1995; 13(4): 295–8.

134. Sepp T, Yates JR, Green AJ. Loss of heterozygosity in tuberous sclerosis hamartomas. J Med Genet 1996; 33(11): 962–4.

135. Green AJ, Johnson PH, Yates JR et al. The tuberous sclerosis gene on chromosome 9q34 acts as a growth suppressor. Hum Mol Genet 1994; 3(10): 1833–4.

136. Argani P, Ladanyi M. Recent advances in pediatric renal neoplasia. Adv Anat Pathol 2003; 10(5): 243–60.

137. Dijkhuizen T, van den Berg E, Storkel S et al. Distinct features for chromophilic renal cell cancer with Xp11.2 breakpoints. Cancer Genet Cytogenet 1998; 104(1): 74–6.

138. Cossu-Rocca P, Eble JN, Delahunt B et al. Renal mucinous tubular and spindle carcinoma lacks the gains of chromosomes 7 and 17 and losses of chromosome Y that are prevalent in papillary renal cell carcinoma. Mod Pathol 2006; 19(4): 488–93.

139. Brandal P, Lie AK, Bassarova A et al. Genomic aberrations in mucinous tubular and spindle cell renal cell carcinomas. Mod Pathol 2006; 19(2): 186–94.

140. Cheuk W, Lo ES, Chan AK et al. Atypical epithelial proliferations in acquired renal cystic disease harbor cytogenetic aberrations. Hum Pathol 2002; 33(7): 761–5.

141. Martignoni G, Brunelli M, Gobbo S et al. Role of molecular markers in the diagnosis and prognosis of renal cell carcinoma. Anal Quant Cytol Histol 2007; 29: 41–9.

142. Martignoni G, Pea M, Chilosi M et al. Parvalbumin is constantly expressed in chromophobe renal carcinoma. Mod Pathol 2001; 14(8): 760–7.

143. Avery AK, Beckstead J, Renshaw AA et al. Use of antibodies to RCC and CD10 in the differential diagnosis of renal neoplasms. Am J Surg Pathol 2000; 24(2): 203–10.

144. Martignoni G, Pea M, Brunelli M et al. CD10 is expressed in a subset of chromophobe renal cell carcinomas. Mod Pathol 2004; 17(12): 1455–63.

145. Abrahams NA, MacLennan GT, Khoury JD et al. Chromophobe renal cell carcinoma: a comparative study of histological, immunohistochemical and ultrastructural features using high throughput tissue microarray. Histopathology 2004; 45(6): 593–602.

146. Adley BP, Papavero V, Sugimura J et al. Diagnostic value of cytokeratin 7 and parvalbumin in differentiating chromophobe renal cell carcinoma from renal oncocytoma. Anal Quant Cytol Histol 2006; 28(4): 228–36.

147. Young AN, de Oliveira Salles PG, Lim SD et al. Beta defensin-1, parvalbumin, and vimentin: a panel of diagnostic immunohistochemical markers for renal tumors derived from gene expression profiling studies using cDNA microarrays. Am J Surg Pathol 2003; 27(2): 199–205.

148. Molinie V, Balaton A, Rotman S et al. Alpha-methyl CoA racemase expression in renal cell carcinomas. Hum Pathol 2006; 37(6): 698–703.

149. Olgac S, Hutchinson B, Tickoo SK et al. Alpha-methylacyl-CoA racemase as a marker in the differential diagnosis of metanephric adenoma. Mod Pathol 2006; 19(2): 218–24.

150. Tretiakova MS, Sahoo S, Takahashi M et al. Expression of alpha-methylacyl-CoA racemase in papillary renal cell carcinoma. Am J Surg Pathol 2004; 28(1): 69–76.

151. Paner GP, Srigley JR, Radhakrishnan A et al. Immunohistochemical analysis of mucinous tubular and spindle cell carcinoma and papillary renal cell carcinoma of the kidney: significant immunophenotypic overlap warrants diagnostic caution. Am J Surg Pathol 2006; 30(1): 13–19.

152. Skinnider BF, Folpe AL, Hennigar RA et al. Distribution of cytokeratins and vimentin in adult renal neoplasms and normal renal tissue: potential utility of a cytokeratin antibody panel in the differential diagnosis of renal tumors. Am J Surg Pathol 2005; 29(6): 747–54.

153. Martignoni G, Brunelli M, Gobbo S et al. Role of molecular markers in the diagnosis and prognosis of renal cell carcinoma. Anal Quant Cytol Histol 2007; 29: 41–9.

154. Gatalica Z, Grujic S, Kovatich A et al. Metanephric adenoma: histology, immunophenotype, cytogenetics, ultrastructure. Mod Pathol 1996; 9(3): 329–33.

155. Pea M, Bonetti F, Zamboni G et al. Melanocyte-marker-HMB-45 is regularly expressed in angiomyolipoma of the kidney. Pathology 1991; 23(3): 185–8.

156. Ladanyi M, Lui MY, Antonescu CR et al. The der(17)t(X;17)(p11;q25) of human alveolar soft part sarcoma fuses the TFE3 transcription factor gene to ASPL, a novel gene at 17q25. Oncogene 2001; 20(1): 48–57.

157. Flocks RH, Kadesky MC. Malignant neoplasms of the kidney; an analysis of 353 patients followed five years or more. J Urol 1958; 79(2): 196–201.

158. Hafez KS, Fergany AF, Novick AC. Nephron sparing surgery for localized renal cell carcinoma: impact of tumor size on patient survival, tumor recurrence and TNM staging. J Urol 1999; 162(6): 1930–3.

159. Robson CJ, Churchill BM, Anderson W. The results of radical nephrectomy for renal cell carcinoma. J Urol 1969; 101(3): 297–301.

159a. Harmer M. TNM Classification of Malignant Tumors, 2nd ed. Geneva, Switzerland: International Union Against Cancer; 1974.

159b. Grene FL, Page D, Morrow M, eds. AJCC Cancer Staging Manual, 6th ed. New York: Springer; 2002.

160. Ficarra V, Schips L, Guille F et al. Multiinstitutional European validation of the 2002 TNM staging system in conventional and papillary localized renal cell carcinoma. Cancer 2005; 104(5): 968–74.

161. Pantuck AJ, Zisman A, Belldegrun AS. The changing natural history of renal cell carcinoma. J Urol 2001; 166(5): 1611–23.

162. Lam JS, Shvarts O, Leppert JT et al. Renal cell carcinoma 2005: new frontiers in staging, prognostication and targeted molecular therapy. J Urol 173(6): 1853–62.

163. Ficarra V, Righetti R, Pilloni S et al. Prognostic factors in patients with renal cell carcinoma: retrospective analysis of 675 cases. Eur Urol 41(2): 190–8.

164. Kontak JA, Campbell SC. Prognostic factors in renal cell carcinoma. Urol Clin North Am 2003; 30(3): 467–80.

165. Ficarra V, Guille F, Schips L et al. Proposal for revision of the TNM classification system for renal cell carcinoma. Cancer 2005; 104(10): 2116–23.

166. Han KR, Bui MH, Pantuck AJ et al. TNM T3a renal cell carcinoma: adrenal gland involvement is not the same as renal fat invasion. J Urol 2003; 169(3): 899–904.

167. Thompson RH, Leibovich BC, Cheville JC et al. Should direct ipsilateral adrenal invasion from renal cell carcinoma be classified as pT3a? J Urol 2005; 173(3): 918–21.

168. Bonsib SM, Gibson D, Mhoon M et al. Renal sinus involvement in renal cell carcinomas. Am J Surg Pathol 2000; 24(3): 451–8.

169. Thompson RH, Leibovich BC, Cheville JC et al. Is renal sinus fat invasion the same as perinephric fat invasion for pT3a renal cell carcinoma? J Urol 2005; 174(4 Pt 1): 1218–21.

170. Thompson RH, Cheville JC, Lohse CM et al. Reclassification of patients with pT3 and pT4 renal cell carcinoma improves prognostic accuracy. Cancer 2005; 104(1): 53–60.

171. Leibovich BC, Cheville JC, Lohse CM et al. A scoring algorithm to predict survival for patients with metastatic clear cell renal cell carcinoma: a stratification tool for prospective clinical trials. J Urol 2005; 174(5): 1759–63; discussion 63.

172. Moinzadeh A, Libertino JA. Prognostic significance of tumor thrombus level in patients with renal cell carcinoma and venous tumor thrombus extension. Is all T3b the same? J Urol 2004; 171(2 Pt 1): 598–601.

173. Lohse CM, Cheville JC. A review of prognostic pathologic features and algorithms for patients treated surgically for renal cell carcinoma. Clin Lab Med 2005; 25(2): 433–64.

174. Terrone C, Cracco C, Porpiglia F et al. Reassessing the current TNM lymph node staging for renal cell carcinoma. Eur Urol 2006; 49(2): 324–31.

175. Heidenreich A, Ravery V. Preoperative imaging in renal cell cancer. World J Urol 2004; 22(5): 307–15.

175a. Novara G, Martignoni G, Artibani W et al. Grading systems in renal cell carcinoma. J Urol 2007; 177(2): 430–6.

176. Fuhrman SA, Lasky LC, Limas C. Prognostic significance of morphologic parameters in renal cell carcinoma. Am J Surg Pathol 1982; 6(7): 655–63.

177. Tsui KH, Shvarts O, Smith RB et al. Prognostic indicators for renal cell carcinoma: a multivariate analysis of 643 patients using the revised 1997 TNM staging criteria. J Urol 2000; 163(4): 1090–5; quiz 295.

178. Ficarra V, Righetti R, Martignoni G et al. Prognostic value of renal cell carcinoma nuclear grading: multivariate analysis of 333 cases. Urol Int 2001; 67(2): 130–4.

179. Frank I, Blute ML, Cheville JC et al. An outcome prediction model for patients with clear cell renal cell carcinoma treated with radical nephrectomy based on tumor stage, size, grade and necrosis: the SSIGN score. J Urol 2002; 168(6): 2395–400.

180. Patard JJ, Leray E, Rioux-Leclercq N et al. Prognostic value of histologic subtypes in renal cell carcinoma: a multicenter experience. J Clin Oncol 2005; 23(12):2763–71.

181. Lanigan D, Conroy R, Barry-Walsh C et al. A comparative analysis of grading systems in renal adenocarcinoma. Histopathology 1994; 24(5): 473–6.

182. Lohse CM, Blute ML, Zincke H et al. Comparison of standardized and nonstandardized nuclear grade of renal cell carcinoma to predict outcome among 2,042 patients. Am J Clin Pathol 2002; 118(6): 877–86.

183. Ficarra V, Martignoni G, Maffei N et al. Original and reviewed nuclear grading according to the Fuhrman system: a multivariate analysis of 388 patients with conventional renal cell carcinoma. Cancer 2005; 103(1): 68–75.

184. Al-Aynati M, Chen V, Salama S et al. Interobserver and intraobserver variability using the Fuhrman grading system for renal cell carcinoma. Arch Pathol Lab Med 2003; 127(5): 593–6.

185. Goldstein NS. The current state of renal cell carcinoma grading. Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC). Cancer 1997; 80(5): 977–80.

186. Cheville JC, Lohse CM, Zincke H et al. Comparisons of outcome and prognostic features among histologic subtypes of renal cell carcinoma. Am J Surg Pathol 2003; 27(5): 612–24.

187. Ljungberg B, Alamdari FI, Stenling R et al. Prognostic significance of the Heidelberg classification of renal cell carcinoma. Eur Urol 1999; 36(6): 565–9.

188. Amin MB, Amin MB, Tamboli P et al. Prognostic impact of histologic subtyping of adult renal epithelial neoplasms: an experience of 405 cases. Am J Surg Pathol 2002; 26(3): 281–91.

189. Moch H, Gasser T, Amin MB et al. Prognostic utility of the recently recommended histologic classification and revised TNM staging system of renal cell carcinoma: a Swiss experience with 588 tumors. Cancer 2000; 89(3): 604–14.

190. Ficarra V, Martignoni G, Galfano A et al. Prognostic role of the histologic subtypes of renal cell carcinoma after slide revision. Eur Urol 2006; 50(4): 786–94.

191. Mian BM, Bhadkamkar N, Slaton JW et al. Prognostic factors and survival of patients with sarcomatoid renal cell carcinoma. J Urol 2002; 167(1): 65–70.

192. Cangiano T, Liao J, Naitoh J et al. Sarcomatoid renal cell carcinoma: biologic behavior, prognosis, and response to combined surgical resection and immunotherapy. J Clin Oncol 1999; 17(2): 523–8.

193. Sengupta S, Lohse CM, Leibovich BC et al. Histologic coagulative tumor necrosis as a prognostic indicator of renal cell carcinoma aggressiveness. Cancer 2005; 104(3): 511–20.

194. Sorbellini M, Kattan MW, Snyder ME et al. A postoperative prognostic nomogram predicting recurrence for patients with conventional clear cell renal cell carcinoma. J Urol 2005; 173(1): 48–51.

195. Uzzo RG, Cherullo EE, Myles J et al. Renal cell carcinoma invading the urinary collecting system: implications for staging. J Urol 2002; 167(6): 2392–6.

196. Palapattu GS, Pantuck AJ, Dorey F et al. Collecting system invasion in renal cell carcinoma: impact on prognosis and future staging strategies. J Urol 2003; 170(3): 768–72; discussion 72.

197. Terrone C, Cracco C, Guercio S et al. Prognostic value of the involvement of the urinary collecting system in renal cell carcinoma. Eur Urol 2004; 46(4): 472–6.

198. Kattan MW, Reuter V, Motzer RJ et al. A postoperative prognostic nomogram for renal cell carcinoma. J Urol 2001; 166(1): 63–7.

199. Zisman A, Pantuck AJ, Dorey F et al. Improved prognostication of renal cell carcinoma using an integrated staging system. J Clin Oncol 2001; 19(6): 1649–57.

200. Zisman A, Pantuck AJ, Wieder J et al. Risk group assessment and clinical outcome algorithm to predict the natural history of patients with surgically resected renal cell carcinoma. J Clin Oncol 2002; 20(23): 4559–66.

201. Han KR, Bleumer I, Pantuck AJ et al. Validation of an integrated staging system toward improved prognostication of patients with localized renal cell carcinoma in an international population. J Urol 2003; 170(6 Pt 1): 2221–4.

202. Ficarra V, Novara G, Iafrate M et al. Proposal for reclassification of the TNM staging system in patients with locally advanced (pT3–4) renal cell carcinoma according to the cancer-related outcome. Eur Urol 2007; 51: 722–9.

202a. Ficarra Vetal Express Validation of the Mayo Clinic Stage, Size, Grade and Necrosis (SSIGN) score to predict cancer specific survival using a European series of conventional renal cell carcinoma. J Urol 2006; 175: 1235–9.

203. Angell SK, Pruthi RS, Merguerian PA. Pediatric genitourinary tumors. Curr Opin Oncol 1996; 8(3): 240–6.

204. Fichtner J, Dairiki Shortliffe LM. Pediatric genitourinary tumors. Curr Opin Oncol 1993; 5(3): 530–7.

205. Julian JC, Merguerian PA, Shortliffe LM et al. Pediatric genitourinary tumors. Curr Opin Oncol 1995; 7(3): 265–74.

206. Merguerian PA, Chang B. Pediatric genitourinary tumors. Curr Opin Oncol 2002; 14(3): 273–9.

207. Prowse OA, Reddy PP, Barrieras D et al. Pediatric genitourinary tumors. Curr Opin Oncol 1998; 10(3): 253–60.

208. Ramphal R, Pappo A, Zielenska M et al. BY. Pediatric renal cell carcinoma: clinical, pathologic, and molecular abnormalities associated with the members of the mit transcription factor family. Am J Clin Pathol 2006; 126(3): 349–64.

209. Lowe LH, Isuani BH, Heller RM et al. Pediatric renal masses: Wilms tumor and beyond. Radiographics 2000; 20(6): 1585–603.

210. Strouse PJ. Pediatric renal neoplasms. Radiol Clin North Am 1996; 34(6): 1081–100.

211. Shamberger RC. Pediatric renal tumors. Semin Surg Oncol 1999; 16(2): 105–20.

212. Neville HL, Ritchey ML. Wilms' tumor. Overview of National Wilms' Tumor Study Group results. Urol Clin North Am 2000; 27(3): 435–42.

213. Beckwith JB. Wilms' tumor and other renal tumors of childhood: a selective review from the National Wilms' Tumor Study Pathology Center. Hum Pathol 1983; 14(6): 481–92.

214. Bisceglia M, Carosi I, Vairo M et al. Congenital mesoblastic nephroma: report of a case with review of the most significant literature. Pathol Res Pract 2000; 196(3): 199–204.

215. Dal Cin P, Lipcsei G, Hermand G et al. Congenital mesoblastic nephroma and trisomy 11. Cancer Genet Cytogenet 1998; 103(1): 68–70.

216. Argani P, Perlman EJ, Breslow NE et al. Clear cell sarcoma of the kidney: a review of 351 cases from the National Wilms Tumor Study Group Pathology Center. Am J Surg Pathol 2000; 24(1): 4–18.

217. White FV, Dehner LP, Belchis DA et al. Congenital disseminated malignant rhabdoid tumor: a distinct clinicopathologic entity demonstrating abnormalities of chromosome 22q11. Am J Surg Pathol 1999; 23(3): 249–56.

218. Weeks DA, Beckwith JB, Mierau GW et al. Rhabdoid tumor of kidney. A report of 111 cases from the National Wilms' Tumor Study Pathology Center. Am J Surg Pathol 1989; 13(6): 439–58.

219. Sostre G, Johnson JF, 3rd, Cho M. Ossifying renal cell carcinoma. Pediatr Radiol 1998; 28(6): 458–60.

Section 2

Adrenal glands

Marina Scarpelli

Normal adrenal gland

Normal adult adrenal glands are composed of cortex and medulla. Embryologically, the adrenal cortex develops from the mesoderm while the medulla takes origin from primitive neuroectodermal cells. The adrenal cortex secretes three classes of steroid hormones: glucocorticoids, mineralocorticoids, and sex steroids. The adrenal medulla secretes predominantly epinephrine. The weight of the gland varies with age and functional status and, according to different sources, ranges between 4 and 6 g in normal adults.[1] When sectioned perpendicular to the long axis the cortex is 1–2 cm thick and bright yellow due to the lipid content, while the medulla is gray-white and concentrated in the head and body of the gland.

Microscopically, the cortex is subdivided into three zones: zona glomerulosa, zona fasciculata, and zona reticularis. Mineralocorticoids are produced in the zona glomerulosa, glucocorticoids in the zona fasciculata, and sex steroids in the zona reticularis. The zona fasciculata makes up about 70% of the cortex and is formed by cords of cells with abundant lipid-filled cytoplasm and is responsible for the bright yellow color of the cortex. The cells of the zona reticularis have lipid-poor cytoplasm and usually contain variable amounts of lipochrome pigment which contribute to its brown color. The zona glomerulosa is a thin and discontinuous subcapsular rim of cells having scant, lipid-poor cytoplasm. The medulla is made of round cells with basophilic cytoplasm (chromaffin cells) arranged in nests and anastomosing cords. At the periphery of the nests there are spindle cells known as sustentacular cells. Ganglion cells are also found with variable frequency. The junction between the cortex and medulla is mostly smooth, but nodules of chromaffin cells can be seen normally in the cortical mantle and islands of cortical cells usually surround the central vein.

The arterial blood supply is offered by the inferior phrenic artery, aorta, and renal artery. The arteries in the capsule divide to give rise to capsular capillaries which are in continuity with the sinusoids of the zonae glomerulosa, fasciculata, and reticularis. The capsular arteries also branch into medullary arteries which traverse the cortex before opening into capillaries in the medulla. Direct connections between cortical and medullary sinusoids have been demonstrated by the use of immunohistochemical markers for endothelial cells.[2]

Innervation is offered by large nerve trunks extending to the medulla; nerve bundles and individual nerve fibers have also been demonstrated by immunohistochemistry in the cortex as well as in the medulla.[3] In the adrenal cortex of adult patients it is not unusual to observe some nodularity. Most commonly, small nodules of 1–3 mm completely or partially surrounded by a fibrous capsule are seen protruding in the periadrenal adipose tissue; they can lie completely free in the adipose tissue and are referred to as extrusions or accessory cortical nodules.

Optimal information can be obtained from the adrenalectomy specimens by using a standardized approach (see Appendix).[4]

Incidental adrenal masses

Incidental adrenal masses, also known as incidentalomas, are discovered during diagnostic testing for a pathologic condition unrelated to an adrenal disorder or at autopsy. Adrenal nodules of 1 to 2 cm are found in 2–3% of adults older than 50 years of age who are examined at autopsy and are particularly frequent in patients with hypertension, obesity, and diabetes mellitus. The prevalence of these incidental nodules increases with age and approaches 7% among people older than 70 years of age. Conversely, it is less than 1% in patients younger than 30 years of age.[5] The prevalence of incidentally discovered adrenal masses and the likelihood of underlying pathologies vary according to the defining criteria. In studies of the general population, most incidentally discovered adrenal masses are adrenocortical adenomas while adrenal medullary tumors are less frequent and are represented mainly by pheochromocytomas. The reported prevalence of adrenal adenomas and nodules in autopsy and tissue pathology series varies widely, reflecting the fact that a sharp distinction between accessory cortical nodules, nodular hyperplasia, and true adenomas cannot always be made on morphologic basis. The inconsistency most significantly impacts on the reporting of small lesions of less than 1 cm.[6]

The prevalence of primary adrenal cortical carcinoma is related mainly to the size of the nodule. The risk increases from 2% for tumors less than or equal to 4 cm to 25% for tumors greater than 6 cm. Neoplasms from 4 to 6 cm in size have a risk of 6% of being a carcinoma. Other adrenal lesions such as myelolipomas, lipomas, cysts, ganglioneuromas, hemangiomas, angiosarcomas, and lymphomas are exceptional. The prevalence of metastases varies in different series, accounting for about 2% in studies not including cancer patients and 30–70% in series including patients with known extra-adrenal cancers. Recent reports suggest that up to 20% of patients with adrenal incidentalomas have some hormonal dysfunction, subclinical hypercortisolism being the most common. The recently proposed term of subclinical autonomous glucocorticoid hypersecretion (SAGE) defines an autonomous cortisol secretion by an adrenal tumor in patients without symptoms of Cushing's syndrome. Given the high prevalence of this condition and the significance of hypertension and diabetes as causes of cardiovascular diseases the management of clinically inapparent adrenal masses is an important aspect of health care.[7] The best diagnostic approach is to use an algorithm that includes an endocrine work-up and imaging by CT or MRI. Surgery is the best choice for lesions with apparent

hypersecretion, suspect for malignancy, or larger than 6 cm (Table 2.1). The use of fine needle aspiration biopsy performed under either CT or US guidance is not recommended as a standard procedure in the diagnostic work-up. However, it may be helpful in the diagnostic evaluation of patients with a history of malignancy.[8]

Adrenal nodular hyperplasia

Adrenal nodular hyperplasia can be found in the setting of a pituitary-dependent or -independent ACTH overproduction. Macronodular hyperplasia occurs in 10–20% of patients with Cushing's disease caused by a pituitary adenoma and, in some patients, the dominant macronodule is monolateral, thus mimicking an adrenal cortical adenoma. Patients with Cushing's disease and macronodular hyperplasia are significantly older and with a longer duration of disease than patients with diffuse hyperplasia[9] (Figures 2.1 and 2.2).

ACTH-independent macronodular adrenal hyperplasia (AIMAH) can be discovered either incidentally or because of the investigation of an adrenal hypersecretion syndrome, mainly Cushing's syndrome. On CT scan the adrenal glands show bilateral nodular enlargement. The asymmetric appearance of adrenal macronodules in AIMAH has been described and may lead to the erroneous diagnosis of unilateral autonomous adenoma.[10] The combined adrenal weight is usually greater than 60 g and can be more than 200 g/gland. On cut sections the nodules are bright yellow to orange and, on microscopic examination, are composed of lipid-rich cortical cells and nests of cells with compact, lipid-poor cytoplasm. Most patients with AIMAH seem to have an aberrant stimulation of cortisol, suggesting the expression of an illicit receptor in their adrenal glands.[11]

Primary pigmented nodular adrenocortical disease (PPNAD) is observed in children and young adults, with a peak during the second decade in patients with Carney complex, i.e. a dominantly inherited syndrome having spotty skin pigmentation, endocrine overactivity, and cardiac myxomas.[12] Adrenal glands from patients with PPNAD are usually normal in size and weigh between 4 and 17 g. Macroscopically there are multiple cortical black nodules, usually less than 2 mm in diameter; the internodular cortex is atrophic (Figure 2.3). Macronodules up to 3 cm have been described, particularly in older patients,[13] and should be distinct from bilateral adenomas. Microscopically the

Table 2.1 Algorithm for practical management of incidental/ adrenal massess.

Figure 2.1
Serial sections of adrenal cortical hyperplasia incidentally detected in a patient with hypertension. The adrenal weight was 13.53 g and the maximum diameter was 6.5 cm. The nodules are bright yellow and confluent.

Figure 2.2
Adrenal hyperplasia found in a patient with a previous diagnosis of colic adenocarcinoma. Nodular enlargement of the gland was detected 3 years later and was initially interpreted as metastatic disease.
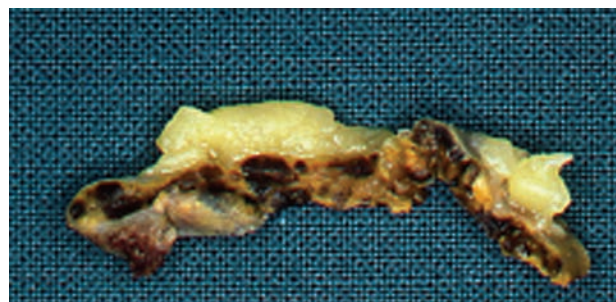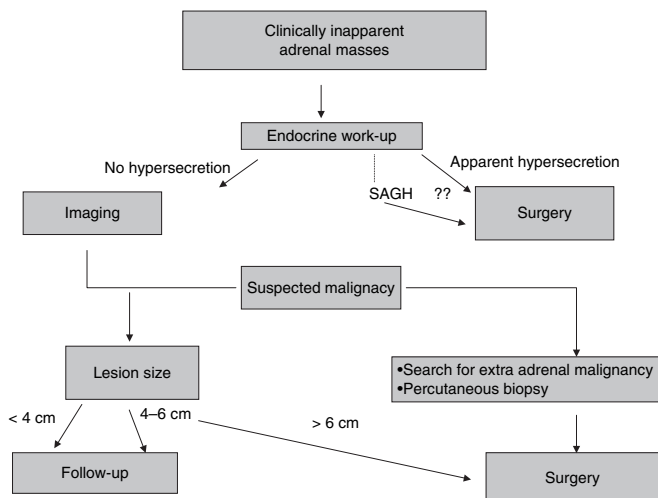

Figure 2.3
Primary pigmented nodular adrenocortical disease in a 27-year-old female patient without clinical signs of Carney complex. The adrenal cortex is studded by deep brown nodules. The internodular cortex is atrophic.

cells have compact, eosinophilic cytoplasm and abundant brown pigment with staining characteristics consistent with lipofuscin; small clusters of lipid-rich cells may be present.

Cortical tumors

Adenoma

Adrenocortical adenomas (ACAs) are benign cortical neoplasms most often associated with functional activity. They are typically unilateral and solitary. Exceptional cases of bilateral adenomas associated with Cushing's syndrome or primary aldosteronism have been published.[14, 15] The most frequent endocrine abnormality associated with adenoma is hyperaldosteronism followed by Cushing's syndrome and virilization. The hypersecretion may manifest as a fully developed endocrine syndrome or by abnormal laboratory data. On CT, adrenal adenomas are generally small, homogeneous, well-defined lesions with clear margins. Frequently they contain large amounts of intracytoplasmic lipids which allows a quantitative evaluation by measurement of the attenuation value on unenhanced CT, while delayed enhanced CT is particularly sensitive for adenomas that are lipid-poor.[16–18] MRI is equally effective since adenomas exhibit a signal drop on chemical shift imaging and have an intensity similar to that of liver on T2-weighted sequences.[19]

Macroscopically a cortical adenoma appears as a sharply circumscribed or encapsulated nodule. It is practically impossible to predict the associated endocrine syndrome on the basis of morphology even though some features are most frequently associated with tumors producing a specific endocrine syndrome.

Adenomas associated with hyperaldosteronism tend to be homogeneous, yellow-orange or canary yellow, small, often 2 cm or less, and weigh less than 10 g. The residual adrenal cortex is not atrophic and shows some micronodules (Figures 2.4 and 2.5). Adrenal cortical adenomas associated with Cushing's syndrome can be homogeneous yellow but often have irregular foci of dark discoloration (Figure 2.6). They tend to be larger than ACAs in hyperaldosteronism, with a mean diameter of 3.5 cm and a weight between 10 and 40 g. Very rarely the tumors are diffusely pigmented and are referred to as 'black adenomas' (Figure 2.7). Most black adenomas are associated with Cushing's syndrome, but a few have been associated with primary hyperaldosteronism.[20]

Figure 2.5
Adenoma associated with hyperaldosteronism. This adenoma is pale yellow and has some suggestion of multinodularity. The remaining cortex is not atrophic and shows some micronodules.

Figure 2.6
Adenoma in Cushing's syndrome. This adenoma measured 3.5 cm and the weight was 16 g. The tumor has well defined contours and is yellow with multiple areas of brown discoloration. The residual cortex is atrophic.

Figure 2.4
Adenoma associated with hyperaldosteronism. This adenoma measured 1.5 cm and the weight was 13 g. The nodule is homogeneous, bright yellow, and appears to be capsulated. The remaining cortex is atrophic.
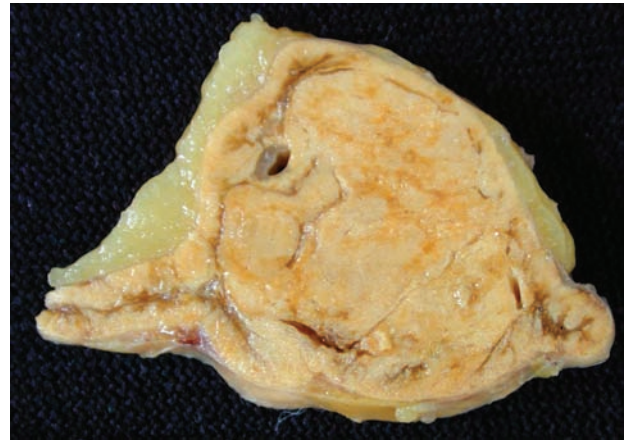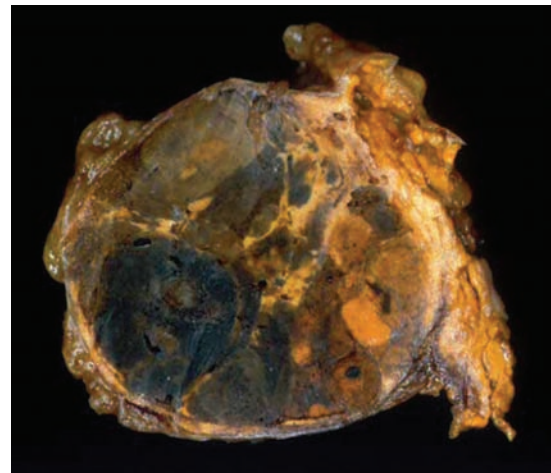

Figure 2.7
This black adenoma was resected from a 60-year-old female with Cushing's syndrome. The nodule measured 2.8 cm and showed pigmented, vaguely nodular areas intermixed with a few yellow spots.

Microscopically most adenomas have smooth borders but they are only rarely surrounded by a complete capsule. They grow forming small nests or alveolar structures and, less frequently, cords and trabeculae. The cells have mostly clear, lipid-rich cytoplasm, resembling the zona fasciculata, with a variable number of cells having compact, eosinophilic cytoplasm similar to the zona reticularis (Figures 2.8 and 2.9). They may contain variable amount of lipochrome pigment in the cytoplasm, especially seen in 'black adenomas'. Hybrid cells with cytologic features of both zonae glomerulosa and fasciculata are also described, mainly in adenomas associated with hyperaldosteronism.[21]

Oncocytic transformation of the cells, foci of lipomatous or myelolipomatous metaplasia, and aggregates of mature lymphocytes are occasionally seen and are particularly frequent in ACAs associated with Cushing's syndrome. There may be a mild degree of nuclear pleom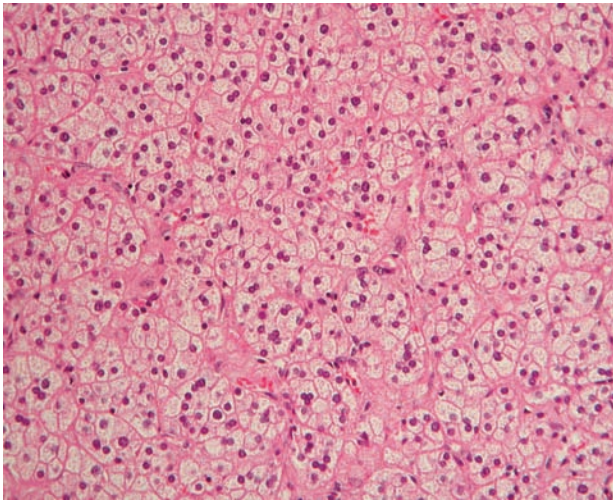orphism. Mitoses are exceptional. The residual adrenal gland is mostly atrophic in ACAs associated with Cushing's syndrome while it frequently shows hyperplasia of the zona glomerulosa and small nodules in ACAs associated with hyperaldosteronism. It has been suggested that the small cortical nodules could be incidental non-hyperfunctional nodules related to the effects of hypertension.[22] The main differential diagnosis includes hyperplastic nodules and adrenal cortical carcinoma. As already pointed out, the differential diagnosis with hyperplastic nodules is sometimes difficult or even impossible exclusively on a morphologic basis. Different approaches have been proposed to solve the problem. Studies on tumor clonality showed that adrenal cortical hyperplasias consist of a polyclonal population of cells while adenomas are mainly monoclonal.[23–25] However, there are exceptions in both groups. A correlation has been observed between clonal patterns and apoptosis and proliferation. Diaz-Cano et al[26] observed that polyclonal lesions demonstrated increasing apoptosis as a counterpoise to rising proliferative rates while monoclonal lesions had progressively lower apoptotic rates as proliferation increased.

Figure 2.8
Classical microscopic appearance of adrenal adenoma. The cells have clear, lipid-rich cytoplasm resembling the zona fasciculata and are organized in small nests separated by scant connective-vascular stroma.
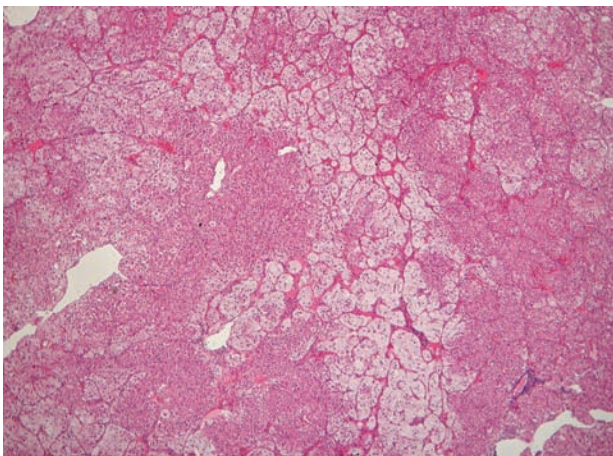

Figure 2.9
Areas of lipid-rich cells are intermixed with areas of lipid-poor cells having eosinophilic cytoplasm in this Cushing's adenoma.

Carcinoma

Adrenocortical carcinoma (ACC) is rare with an approximate incidence rate of 0.5–2 cases per million persons per year in the USA. The mean age at diagnosis ranges between 20 and 54 years in different series, probably reflecting the type of endocrine service reporting. In most of the series the peak of incidence is in the fourth and fifth decade. In some series, where pediatric cases are included, a peak in the first decade has been observed.[27] As for the gender, in most series a female prevalence has been reported. A variable percentage of carcinomas, ranging from 24 to 96%, is functioning. The most common clinical presentation is a mixed hormonal syndrome of hypercortisolism and virilization and, less commonly, a pure Cushing's syndrome. The syndrome of isolated primary hypermineralocorticism is quite rare. Non-functioning carcinomas may present with abdominal pain, palpable tumor mass, weight loss, weakness, non-specific gastrointestinal symptoms, and myalgias. Adrenal carcinoma can be associated with other tumors, in particular breast carcinoma, thyroid carcinoma, and melanoma, with a frequency between 12 and 37%.[28] Bilateral cortical carcinoma is extremely rare. Most carcinomas are sporadic but they can be part of several familial or sporadic genetic syndromes such as Li–Fraumeni syndrome, Beckwith–Wiedemann syndrome, and Multiple Endocrine Neoplasia Type 1.[29] Adrenal carcinomas represent 5% of incidentalomas and mostly are non-functioning. CT demonstrates usually large, dense, irregular, heterogeneous, enhancing lesions. Calcification and necrosis are common. Malignant tumors less than 6 cm are often homogeneous and may resemble adenomas. MRI hyperintense signal on T2-weighted images and avid enhancement with delayed signal are common features in carcinomas as well as in adrenal metastases.[30]

Weight and size have important prognostic implications. Malignancy risk rises with the size and weight of the tumor. Weight above 100 g was the most useful criterion in the series of Tang and Gray[31] to distinguish benign from malignant tumors. In the series of Aubert et al which included 24 malignant tumors a weight ≥50 g and a tumor size ≥6.5 were significant for malignancy with 100% sensitivity and more than 90% specificity.[32] However, exceptions do exist and, as a consequence, tumor size may only have a guiding value in the assessment of adrenocortical malignancy. The cut surface generally shows a variegate pattern and is multinodular with individual nodules being soft and friable. Areas of hemorrhage and necrosis are common (Figures 2.10 and 2.11). The capsule is often
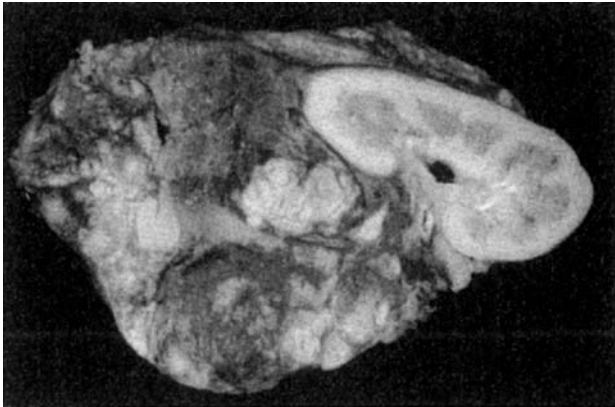
Figure 2.10
This overly malignant carcinoma measured 15 cm, invaded the perirenal adipose tissue, and had multiple areas of hemorrhage and necrosis. The kidney is not infiltrated in this image.
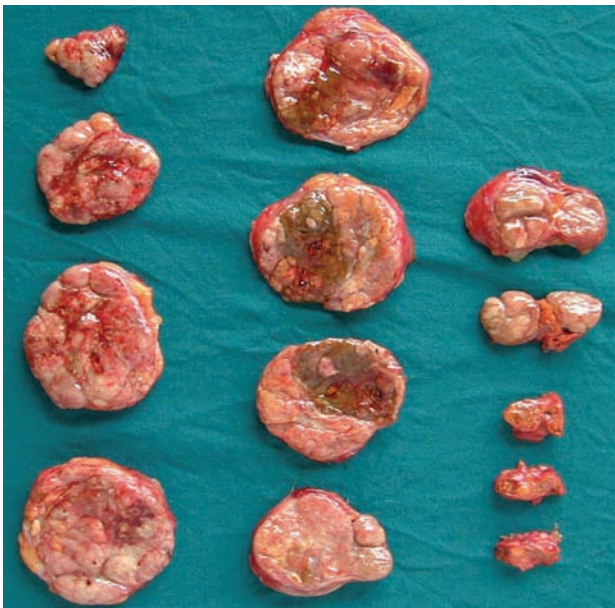
Figure 2.11
This localized carcinoma measured 7.5 cm and weighed 95 g. The cut surface is multinodular with myxoid areas.

Figure 2.12
Microscopic appearance of adrenocortical carcinoma. The tumor grows in a diffuse and trabecular pattern. The cells have mostly eosinophilic cytoplasm; small groups of cells with lipidization of the cytoplasm are identifiable at this low-power magnification.
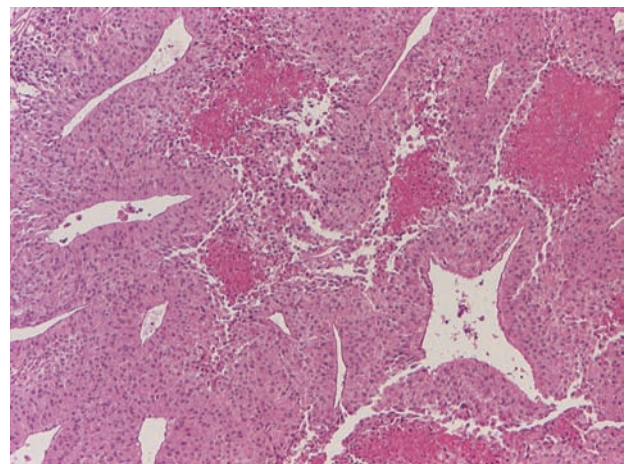
Figure 2.13
Multiple foci of necrosis give to this carcinoma a pseudopapillary pattern. The vascular support is given by gaping sinusoids.

infiltrated and the tumor can invade adjacent organs or tissues. Most of the larger tumors can be correctly assumed to be malignant based upon gross inspection alone. Smaller ACCs may not be as heterogeneous (Figures 2.10 and 2.11). Microscopically, most carcinomas have an architectural pattern that can be classified as trabecular, alveolar, or diffuse, the trabecular pattern being the most characteristic and common. Some rare cases are mainly myxoid while others are pseudoglandular. Most cells are lipid-poor with compact eosinophilic cytoplasm, but lipid-rich cells can be present. Occasionally, coarse granular pigment is seen within the cytoplasm. Nuclear pleomorphism and hyperchromasia can be striking. Mitotic figures are relatively common and can be atypical. Vascular invasion, venous or sinusoidal, and capsular invasion are common in the larger examples (Figures 2.12 and 2.13). Immunohistochemistry can be used in morphologically undifferentiated tumors to differentiate ACC from metastases and also to distinguish adrenocortical from medullary lesions. Adrenal carcinomas usually express vimentin, low molecular weight cytokeratin, inhibin α-subunit, calretinin, and melan-A.[33] A high percentage of adrenal carcinomas expresses synaptophysin.[34] Adrenal carcinomas are constantly negative for cromogranin and CD10 and these results help to differentiate pheochromocytoma and metastatic renal cell carcinoma[35] (Figures 2.14–2.16).

Numerous alterations of gene regulation and expression have been described in sporadic adrenocortical carcinomas but they are difficult to place in a context of tumor formation and progression and to apply to clinical practice.

A germline TP53 mutation in exon 10 (R337H) has been described in Brazilian children with either adenomas or carcinomas but no other identifiable clinical syndrome.[36] The same mutation has been identified in adult Brazilian patients harboring adrenal tumors. It is now acknowledged that the R337H mutation is a signature, low-penetrance allele causing an exclusive predisposition to ACC.[37]
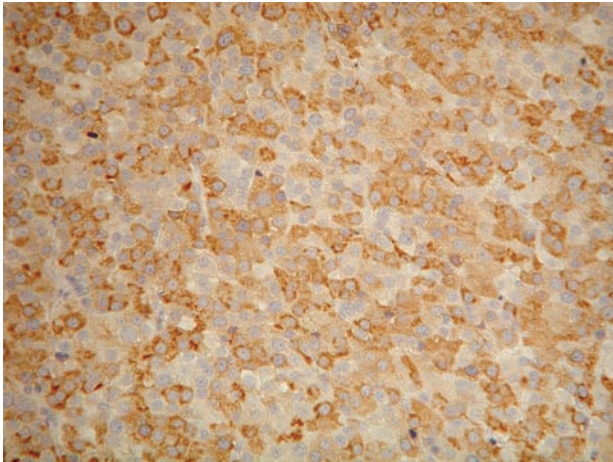
Figure 2.14
Intense and diffuse cytoplasmic staining for inhibin α-subunit in adrenocortical carcinoma.
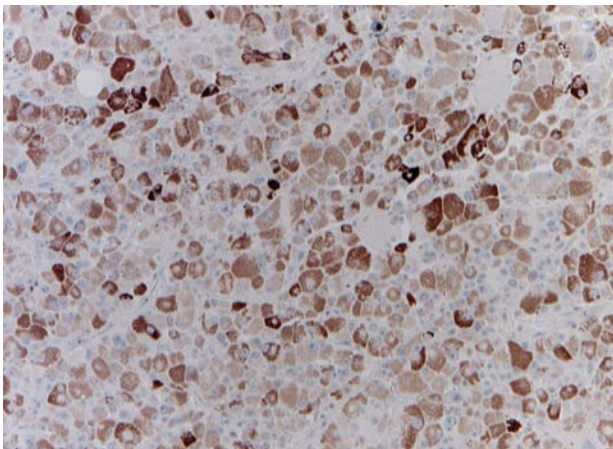
Figure 2.15
Dishomogeneous staining for melan-A antibody in another example of adrenocortical carcinoma.
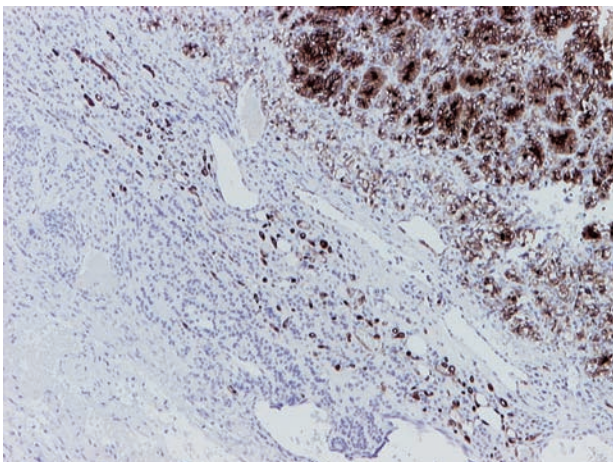
Figure 2.16
CD10 decorates the cytoplasm of the cells in a case of metastatic renal cell carcinoma. The residual adrenal cortex is not stained.

Other studies showed mutations in exons 5–8 of TP53 in 20–27% of ACCs.[38, 39] Barzon et al[40] found TP53 mutations in tumor DNA in 70% of their adrenocortical carcinomas. LOH at the 17p13 where the TP53 gene is located has been shown to be a strong predictor of shorter disease-free survival in patients with sporadic adrenocortical tumors.[41] By immunohistochemistry p53 positivity has been reported in an extremely variable percentage of carcinomas, ranging from 0.7 to 93%, thus making this marker not very useful to discriminate between benign and malignant tumors.[42]

Other specific gene alterations have been found at 11p15.5 where the IGF-II, H19, and p57/KIP2 genes are mapped. H19 and IGF-II have been found to show coordinate, reciprocal regulation. Altered DNA methylation of the H19 promoter seems to be involved in the abnormal expression of both H19 and IGF-II genes in human adrenocortical carcinomas.[43]

The insulin-like growth factor II (IGFII) gene is upregulated in adrenocortical carcinomas and IGFII was shown to be overexpressed by RNA array analysis. Schmitt et al,[44] using immunohistochemistry, demonstrated the expression of IGFII in 76.5% of carcinomas and 4.5% of adenomas as a perinuclear or Golgi pattern immunoreactivity, while in the series by Erickson et al,[45] 92.5% of carcinomas and 54.7% of adenomas were immunoreactive.

In the absence of metastases or obvious local invasion the diagnosis of carcinoma is based mainly on histopathologic criteria. Several multiparametric systems have been described, the one proposed by Weiss in 1984 being the most widely used.[46] It is based on the following nine criteria: high nuclear grade, mitotic figures >5/50 high-power fields, atypical mitotic figures, eosinophilic or compact tumor cell cytoplasm, diffuse architecture, necrosis, venous invasion, sinusoidal invasion, and capsular invasion. The presence of three or more of these criteria is considered significant for a malignant clinical behavior.[47] The main drawback is that the interpretation and application of Weiss histopathologic criteria can be difficult and subjective. In the experience of Sasano et al,[48] nuclear grade, architecture, and cytoplasm had a rather low interobserver reproducibility. Furthermore, these criteria are not useful to discern malignancy in pediatric cases and in oncocytic tumors. In the series of Aubert et al[32] the most reliable criteria were considered mitotic rate and necrosis, while abnormal mitoses, cytoplasm, and capsular invasion were slightly less reliable. Additional markers of malignancy have been proposed more recently to achieve more precise diagnosis. Proliferative activity measured by MIB1 staining is significatively higher in carcinomas, but there is uncertainty concerning the significant threshold. Wachenfeld et al[49] found that a cut-off level of 5% separated benign from malignant adrenocortical tumors without overlap. By using the same cut-off level, Schmitt et al obtained a discrimination between benign and malignant tumors with a sensitivity of 87.5% and a specificity of 95.5%.[44] Lower degrees of sensitivity and specificity have been reported by others.[50]

The most widely used staging system for adrenocortical carcinoma was originally proposed by MacFarlane[51] and modified by Sullivan et al.[52] The staging system for adrenal carcinoma is reported in Table 2.2.[53] The correlation between stage and survival after diagnosis demonstrated no differences in patients with stage I or II tumors, but survival was greatly reduced in patients with stage IV tumors and distant metastases or invasion in adjacent organs. Patients with stage I or II tumors have the best chance of cure with complete surgical excision.

From a pathologic point of view, low mitotic rate and a low tumor proliferative fraction evaluated by MIB1 antibody are considered favorable features. From a genetic point of view, 17p13 LOH and overexpression of the IGFII gene are strong predictors of shorter disease-free survival.

Table 2.2 Staging criteria for adrenal cortical carcinoma

Stage	Criteria
TNM definitions	
Tumor	
T1	Tumor ≤5 cm, invasion absent
T2	Tumor >5 cm, invasion absent
T3	Tumor outside adrenal in fat
T4	Tumor invading adjacent organs
Lymph nodes	
N0	No positive lymph nodes
N1	Positive lymph nodes
Metastases	
M0	No distant metastases
M1	Distant metastases
Stage grouping	
I	
II	T2, N0, M0
III	T1–2, N1, M0; T3, N0, M0
IV	Any T, any M, M1; T3, T4, N1

Oncocytic adrenocortical neoplasms

Oncocytic adrenocortical neoplasms are composed predominantly or exclusively of polygonal oncocytes with abundant granular and intensely eosinophlic cytoplasm packed with mitochondria. They are extremely rare and only small series or single case reports have been published in the literature. Most cases are non-functional, with single cases associated with virilization or Cushing's syndrome. The majority arises in females between 40 and 50 years of age (mean 47.6). They are well-circumscribed tumors ranging in size from 3 to 15 cm (mean 8 cm) and with a mean weight of 281 g (Figure 2.17). Histologically the neoplastic cells are arranged in a diffuse or solid pattern. Stromal degenerative changes are particularly frequent in larger tumors. Nuclear atypia, characterized by enlarged nuclei with prominent nucleoli, multinucleation, irregular nuclear contours, nuclear pseudoinclusions, and hyperchromatic chromatin, are frequent findings[54] (Figure 2.18). As for the biological behavior either oncocytomas or oncocytic neoplasms of uncertain malignancy potential or carcinomas have been reported. The differential diagnosis between benign oncocytomas and oncocytic carcinomas can be difficult. In general, benign tumors do not have necrosis, capsular and/or vascular invasion, and mitoses are less than 2 per 50 HPF. In a series of four oncocytic adrenocortical carcinomas, Hoang et al [55] stated that cytologic atypia or mitotic rate cannot reliably predict the biologic behavior. They considered features of malignancy to be large tumor size, extracapsular extension, blood vessel invasion, necrosis, and metastasis. In their series of 10 adrenocortical oncocytic tumors including four carcinomas, Bisceglia et al[56] adopted major criteria (high mitotic rate, atypical mitoses, and venous invasion) and minor criteria (large size, necrosis, capsular invasion, and sinusoidal invasion) to distinguish benign and malignant tumors. They suggested that the presence of one major criterion indicated malignancy.

Myelolipoma

Myelolipomas are rare tumors composed of mature fat associated with hematopoietic elements. The estimated incidence at autopsy
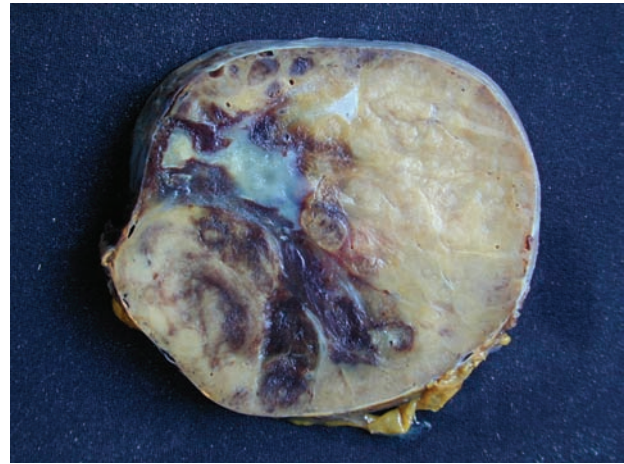
Figure 2.17
Adrenal oncocytoma. This well-circumscribed nodule measured 6 cm. The tumor is light brown, similar to oncocytomas in other anatomic sites. Regressive areas are present.
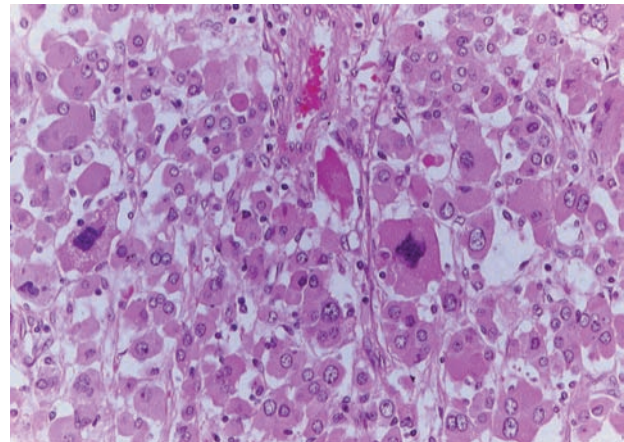
Figure 2.18
Oncocytoma with solid pattern and striking cytologic atypia.

varies from 0.08 to 0.2%. Most are asymptomatic and diagnosed either as incidental radiologic or post-mortem findings. Larger lesions may present with symptoms, occasionally having significant retroperitoneal hemorrhage. They are usually diagnosed in the late adult life without sex differences. Association with other adrenal conditions, mainly adenomas, occurs in 5–15% of cases. Very rarely, patients with thalassemia or myelofibrosis present with masses of extramedullary hemopoiesis in their adrenal glands.

The mean diameter is usually less than 4 cm but giant tumors, up to 35 cm and weighing more than 5000 g, have been reported. Macroscopically they are well-circumscribed but rarely encapsulated masses. The color varies from yellow to red-brown depending on the relative amount of adipose and hematopoietic elements (Figure 2.19). On microscopic examination mature adipose tissue is admixed with hematopoietic tissue having trilineage hematopoiesis with normal cell morphology and complete maturation.[57] There are a number of theories on the origin of myelolipomas, the most commonly accepted being that they originate from metaplasia of adrenal cortical cells or from uncommitted or pluripotential adrenal stromal cells. A recent study showed that both the hematopoietic elements and the fat have the same pattern of X-chromosome inactivation, suggesting that

Figure 2.19
Myelolipoma. Mature adipose tissue and red-brown areas corresponding to hemopoietic tissue are easily identified.

Figure 2.20
Pheochromocytoma. This very small tumor in a patient with MEN 2A is completely surrounded by adrenal cortex.

myelolipomas are clonal proliferations derived from a common pluripotential stem cell.[58]

Pheochromocytoma

Pheochromocytomas arise from the sympathoadrenal system, i.e., the adrenal medulla and paraganglion system. It is a widespread assumption that most pheochromocytomas are sporadic and only about 10% are hereditary. Hereditary pheochromocytoma can be a component of multiple endocrine neoplasia type 2, Von Hippel–Lindau disease, and neurofibromatosis type 1. Germ-line mutations of the succinate dehydrogenase gene subunits B and D have been described in a series of non-syndromic, apparently sporadic, pheochromocytomas.[59]

Sporadic pheochromocytomas occur at all ages but are more common in the fourth through sixth decades of life. Women and men are similarly affected. In the majority of the cases they are monolateral, but in 3–11% of cases they are bilateral. Hypertension, sustained or paroxysmal, is the hallmark clinical finding. The diagnosis of pheochromocytoma is established by the demonstration of elevated levels of free catecholamines or their metabolites in urine and blood.[60]

Pheochromocytomas are generally characterized by low T1 and bright T2 signal intensities on MRI. Meta-iodobenzylguanidine (MIBG), a physiologic analog of norepinephrine, is a diagnostic test for pheochromocytoma and is useful for the detection of extra-adrenal, metastatic, and recurrent sites of disease.[61] The size of the tumors is variable, the majority being between 3 and 5 cm but with a tendency for malignant examples to be larger.[62] They are usually encapsulated or well-circumscribed, soft, gray-tan to brown-red masses with a variegated cut surface showing areas of hemorrhage or cystic degeneration. Residual cortex can be seen at the periphery. Some examples show infiltration of the peri-adrenal adipose tissue (Figures 2.20–2.22).

Under light microscopy the neoplastic cells are arranged in spherical, compact nests separated by a scant vascular stroma forming the classic 'zellballen' pattern (Figure 2.23). The cytoplasm is abundant, mostly basophilic and granular. Nuclei are centrally located and oval with finely granular chromatin and small nucleoli. Intracytoplasmatic hyaline globules and eosinophilic proteinaceous material resembling colloid are not uncommon. Cells with multiple nuclei or

Figure 2.21
Characteristic appearance of a pheochromocytoma. The mass is homogeneous, soft, and gray-tan.

prominent hyperchromasia and occasional mitoses are encountered. Unusual features with potential problems for differential diagnosis are represented by a spindle cell or angiomatous pattern or by oncocytic transformation of the cells.[63, 64] By immunohistochemistry all pheochromocytomas are immunoreactive with chromogranin and the majority with synaptophysin (Figure 2.24). S100-positive sustentacular cells are seen at the periphery of the cellular nests. Focal immunoreactivity has been described with cytocheratins 7 and 20. Calretinin and inhibin are constantly negative.[33]
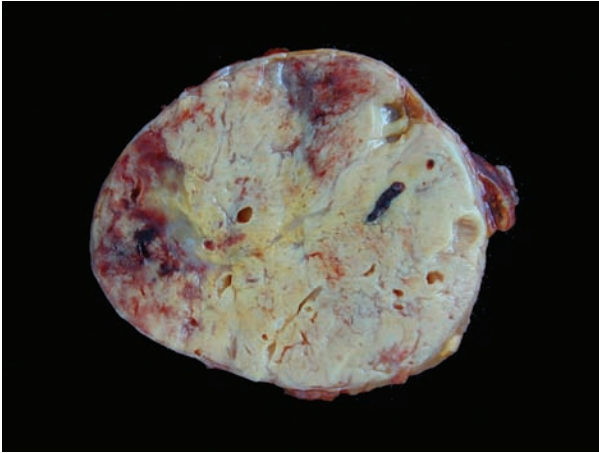
Figure 2.22
This pheochromocytoma has a dishomogeneous cut surface and a few yellow areas suggesting lipid deposits. The presence of lipids was confirmed by histochemistry and electron microscopy.
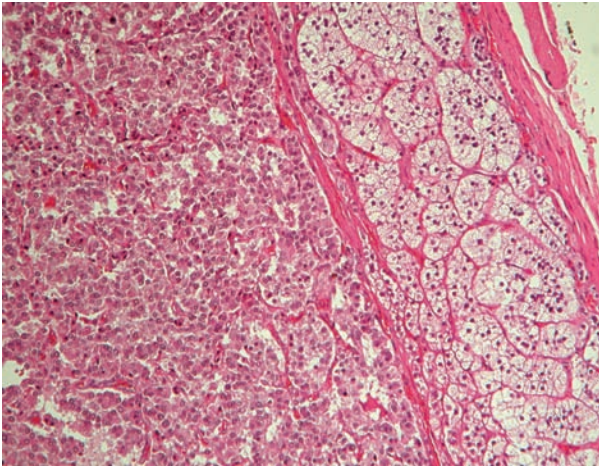

Figure 2.23
Sharp border between adrenal cortex and pheochromocytoma. The tumor forms small and compact nests separated by scant vascular stroma (zellballen pattern).
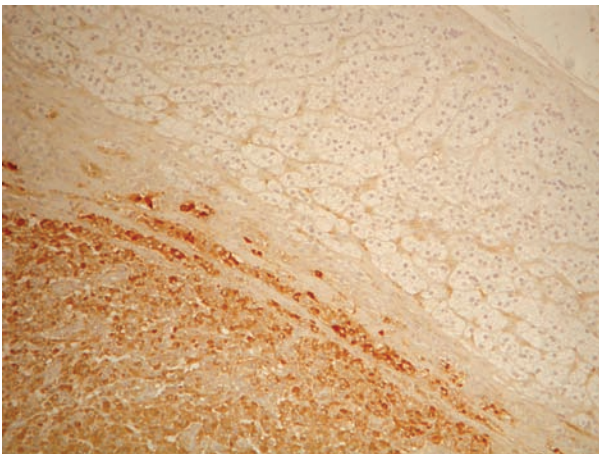
Figure 2.24
Chromogranin stains the pheochromocytoma but not the normal adrenal cortex.

Most pheochromocytomas are benign, slowly growing tumors. The distinction between benign and malignant pheochromocytomas is an unresolved problem and in most cases the decision is based on the occurrence of metastases in sites where chromaffin tissue is not normally found. As a consequence, the percentage of malignant tumors ranges from 2.4 to 26.[65, 66] Although it is commonly believed that the biological behavior of a pheochromocytoma cannot be predicted on the basis of microscopic features, certain histologic features have been associated more frequently with clinically malignant tumors. A Pheochromocytoma of the Adrenal gland Scaled Score (PASS) has been proposed by Thompson[67] to separate benign from malignant tumors. Similar to the Weiss approach for adrenal cortical neoplasms, PASS takes into account several histologic features such as: growth pattern, tumor necrosis, high cellularity, cellular monotony, tumor cell spindling, mitotic figures, atypical mitotic figures, extension into the adipose tissue, vascular invasion, capsular invasion, profound nuclear pleomorphism, and nuclear hyperchromasia. Each feature is given a numerical value when present. In the original series including 50 histologically benign and 50 histologically malignant pheochromocytomas, malignant tumors always had a PASS ≥4. Limitations in the application of this method do exist since it is laborious, there is a certain degree of subjectivity in the evaluation of some of the features, and an intermediate category is not provided. Salmenkivi et al,[68] in their series including 69 adrenal pheochromocytomas, identified the following as suspicious malignant histologic features: mitotic count (over 5 mitoses/10 HPF), necrosis, and vascular and capsular invasion. They considered those tumors that had not metastasized but had at least one suspicious feature as borderline and in need of a closer follow-up.

The growth fraction assessed by immunohistochemistry using MIB1 has shown a significant correlation with metastatic potential with values in most series ≥5%.[69, 70] A number of genetic alterations have been described in sporadic pheochromocytomas and several chromosome regions that may harbor genes critically involved in their pathogenesis have been identified. However, it is not clear how these allele losses are involved in tumorigenesis or tumor progression.[71–73]

Composite pheochromocytoma

The term composite pheochromocytoma is applied to tumors with combined features of ganglioneuroma or ganglioneuroblastoma and typical pheochromocytoma. The majority consist of pheochromocytoma and ganglioneuroma and occur in middle-aged or elderly patients. Tumors having a neuroblastic component may give rise to widespread metastases. Macroscopically they may resemble typical pheochromocytoma, or have pale areas corresponding to the ganglioneuroma, or hemorrhagic areas of ganglioneuroblastoma (Figure 2.25). The ganglioneuromatous component includes a variably abundant Schwannian stroma and ganglion cells (Figure 2.26). Variable amounts of neuromelanin may occasionally be found.[74,75] A percentage of patients with composite tumors have type 1 neurofibromatosis and MEN 2A.

Neuroblastic tumors

Under this term are included neuroblastoma, ganglioneuroblastoma, and ganglioneuroma. Neuroblastoma is the fourth most common malignant tumor in children under 15 years and more than 80% of

Figure 2.25
Gray compact areas and red-brown areas are seen in this composite pheochromocytoma. The gray areas represent ganglioneuroma.
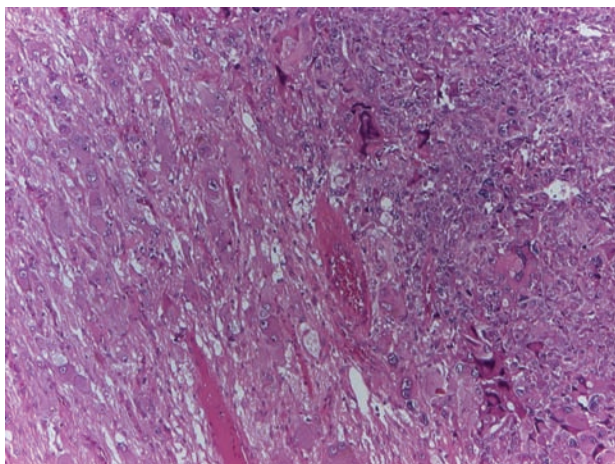
Figure 2.26
Microscopic appearance of a composite pheochromocytoma. The ganglioneuroma on the left is easily identified because of a rich Schwannian stroma and polymorphic ganglion cells. The two components are fairly well separated in this image.

the cases are diagnosed during the first 4 years of life.[1] About 40% of neuroblastomas take origin in the adrenal glands.[76] Clinically there is usually a palpable abdominal mass. A number of paraneoplastic syndromes caused by the production by the tumor of specific substances or by the presence of antibodies against normal cells are not infrequent. Imaging studies by CT or MRI give excellent information about the primary tumor and the state of the regional lymph nodes.[77] A diphosphate bone scan and a MIBG scan are used to assess distant metastases in the bone and bone marrow.[78] Urinary catecholamine secretion is a confirmatory diagnostic marker. Dimensions range from 1 to 10 cm. Macroscopically the tumors are capsulated or well-circumscribed and soft, with frequent areas of hemorrhage and necrosis; calcifications are common (Figure 2.27). With advancing levels of differentiation the tumors may be firmer. Some examples are cystic. The microscopic appearance varies depending on the level of differentiation. Immature neuroblasts are completely undifferentiated small cells and their identification relies on ancillary techniques

Figure 2.27
Neuroblastoma. Multinodular mass with multiple hemorrhagic and necrotic areas.

such as immunohistochemistry, electron microscopy, and molecular biology or cytogenetics. Differentiation is seen as synchronous maturation of the nucleus and cytoplasm toward a ganglion cell phenotype, the appearance of a neuropil, and a Schwannian stroma. There is a veritable continuum between undifferentiated neuroblastomas and well-differentiated, stroma-rich tumors.

According to the International Neuroblastoma Classification[79] four categories are identified:

■ neuroblastoma (Schwannian stroma-poor) including three subtypes: undifferentiated, poorly differentiated, and differentiating;
■ ganglioneuroblastoma intermixed (Schwannian stroma-rich);
■ ganglioneuroma (Schwannian stroma-dominant) including two subtypes: maturing and mature;
■ ganglioneuroblastoma nodular (composite Schwannian stroma-rich/stroma-dominant, and stroma-poor).

Age and stage of disease are two of the most powerful independent prognostic factors for patients with neuroblastoma and ganglioneuroblastoma. The International Neuroblastoma Staging system is based on the size of the primary tumor, locoregional lymph node status, and the presence of distant metastases (Table 2.3). Risk group assessment can be defined by clinical and biological variables. Genetic changes such as the MYCN status (amplified and non-amplified) and the DNA ploidy together with the histology and the International Neuroblastoma Staging System are integrated in the Risk Grouping Scheme where low-, intermediate-, and high-risk groups are identified.[76]

The genetic and morphologic heterogeneity of neuroblastoma requires extensive biological and histologic study of the tumor.[80] See Appendix for details.

Miscellaneous tumors and tumor-like lesions

Adrenal cysts

Adrenal cysts are relatively rare lesions with a predilection for female patients and the fifth and sixth decades. Conventionally they are

Table 2.3 International Neuroblastoma Staging System

Stage 1
  Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymphnodes negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive).

Stage 2A
  Localized tumor with incomplete gross excision; representative ipsilateral nonhaderent lymphnodes negative for tumor microscopically.

Stage 2B
  Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically.

Stage 3
  Unresectable unilateral tumor infiltrating across the midline, with or without regional lymph node involvement or localized unilateral tumor with contralateral regional lymph node involvement or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement.

Stage 4
  Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs (except as defined by stage 4S).

Stage 4S
  Localized primary tumor (as defined for stage 1, 2A or 2B) with dissemination limited to skin, liver, and/or bone marrow. Limited to infants <1 year of age.

divided into four categories: endothelial, hemorrhagic, parasitic, and epithelial.[81] Hemorrhagic (pseudocystic) cysts and endothelial cysts are more common. Dimensions vary greatly and symptoms are usually associated with larger cysts. Immunohistochemistry can be helpful in differentiating endothelial and epithelial lined cysts.[82] In a minority of the cases differential diagnosis is with benign or malignant adrenal tumors undergoing extensive hemorrhagic necrosis.[83]

Adenomatoid tumors

Adenomatoid tumor is a rare neoplasm, usually presenting in male patients as an incidental adrenal mass. Macroscopically these tumors are usually poorly circumscribed. The size ranges from 0.5 to 11 cm.[84] Histologically they consist of tubules and channels arranged in a variably fibrous stroma. The cells lining the tubules are partly epithelioid, with abundant cytoplasm and intracytoplasmic lumina, and partly flattened, resembling endothelial cells. Immunohistochemistry shows strong immunostaining for epithelial and mesothelial markers.[85] The differential diagnosis includes a variety of solid and cystic tumors, primary and metastatic.[86]

Metastases

Adrenal metastases more commonly occur in patients with lung, kidney, breast, and gastrointestinal carcinomas.[87] In the majority of the patients adrenal metastases are discovered within a short period after the detection of the primaries. However, later presentation, after more than 20 years, has been reported for renal cell carcinoma.[88] Unilateral and solitary adrenal metastases are not easily distinguished from primary non-functional adrenal tumors. Fine needle aspiration biopsy may be very helpful in documenting an adrenal metastasis.[8]

Appendix: handling of adrenal gland specimens

When possible, immediately after resection, the intact specimen should be sent unfixed to the pathology laboratory accompanied by a description of the relevant clinical findings, including the clinical history, results of hormonal and imaging studies, and clinical diagnosis.

In the laboratory the following steps should be followed:

- The specimen is oriented.
- A careful dissection of fat tissue is carried out.
- The whole specimen is accurately weighed.
- The dimensions are recorded (possibly along three axes).
- The gland is cut into slices 3–5 mm thick, perpendicular to the long axis.
- The dimensions of the tumor(s) are accurately assessed.
- The macroscopic appearance is described.
- The appearance of the adrenal remnant is also described (atrophy, cortical nodules, etc.).

At this stage fresh tissue for research purposes or other ancillary procedures can be taken. Following formalin fixation adequate sampling should be carried on. One block per cm diameter from the peripheral and central part of the tumor including the margins is considered adequate.

For neuroblastic tumors a slightly different approach is used:

- The specimen should be transferred unfixed to the pathology laboratory under sterile conditions.
- At least two pieces, each measuring $1 \times 1 \times 1$ cm, should be taken from viable looking areas of the tumor. If there are macroscopic differences on the cut surface, pieces should be taken from all these areas.
- Each piece is identified with capitals (A, B, etc.) and divided into fourths identified by numbers (1–4). Samples A1, B1, etc., should be used to make touch preparations and put in formalin for histopathologic examination. Samples A2, B2, etc., should be put in sterile tissue-culture medium. Pieces 3 and 4 should be snap frozen in liquid nitrogen.

References

1. Lack EE. Tumors of the Adrenal Gland and Extra Adrenal Paraganglia. In: Rosai J, ed. Atlas of Tumor Pathology. Rosai J, ed. Third Series Fascicle 19. Washington DC: Armed Forces Institute of Pathology; 1997.
2. Magennis DP, McNicol AM. Vascular patterns in the normal and pathological human adrenal cortex. Virch Arch 1998; 433: 69–73.
3. Li Q, Johansson H, Grimelius L. Innervation of human adrenal gland and adrenal cortical lesions. Virch Arch 1999; 435: 580–9.
4. Scarpelli M, Algaba F, Kirkali Z et al. Handling and pathology reporting of adrenal gland specimens. Eur Urol 2004; 45: 722–9.
5. Barzon L, Sonino N, Fallo F et al. Prevalence and natural history of adrenal incidentalomas. Eur J Endocrinol 2003; 149: 273–85.

6. Kloos RT, Gross MD, Francis IR et al. Incidentally discovered adrenal masses. Endocr Rev 1995; 16: 460–84.

7. Mansmann G, Lau J, Balk E et al. The clinically inapparent adrenal masses: update in diagnosis and management. Endocr Rev 2004; 25: 309–40.

8. Saboorian MH, Katz RL, Charnsangavej C. Fine needle aspiration cytology of primary and metastatic lesions of the adrenal gland. A series of 188 biopsies with radiologic correlation. Acta Cytol 1995; 39: 843–51.

9. Smals AG, Pieters GF, van Haelst UJ et al. Macronodular adrenocortical hyperplasia in long-standing Cushing's disease. J Clin Endocrinol Metab 1984; 58: 25–31.

10. N'Diaye N, Hamet P, Tremblay J et al. Asynchronous development of bilateral nodular hyperplasia in gastric inhibitory polypeptide-dependent Cushing's syndrome. J Clin Endocrinol Metab 1999; 84: 2616–22.

11. Christopoulos S, Bourdeau I, Lacroix A. Clinical and subclinical ACTH-independent macronodular adrenal hyperplasia and aberrant hormone receptors. Horm Res 2005; 64: 119–31.

12. Groussin L, Cazabat L, René-Corail F et al. Adrenal pathophysiology: lessons from the carney complex. Horm Res 2005; 64: 132–9.

13. Travis WD, Tsokos M, Doppman JL et al. Primary pigmented nodular adrenocortical disease. A light and electron microscopic study of eight cases. Am J Surg Pathol 1989; 13: 921–30.

14. Nomura K, Saito H, Aiba M et al. Cushing's syndrome due to bilateral adrenocortical adenomas with unique histological features. Endocr J 2003; 50: 155–62.

15. Engel JD, Angelos P, Rege RV et al. Bilateral adrenal cortical adenomas in primary hyperaldosteronism. Urology 1998; 52: 711–14.

16. Korobkin M, Brodeur FJ, Yutzy GC et al. Differentiation of adrenal adenomas from nonadenomas using CT attenuation values. AJR 1996; 166: 531–6.

17. Boland GW, Hahn PF, Pena C et al. Adrenal masses: characterization with delayed contrast-enhanced CT. Radiology 1997; 202: 693–6.

18. Cirillo RL JR, Bennett WF, Vitellas KM et al. Pathology of the adrenal gland: imaging features. AJR 2000; 170: 429–35.

19. Hönigschnabl S, Gallo S, Niederle B et al. How accurate is MR imaging in characterization of adrenal masses: update of a long-term study. Eur J Radiol 2002; 41: 113–22.

20. Cohen RJ, Brits R, Phillips JI et al. Primary hyperaldosteronism due to a functional black (pigmented) adenoma of the adrenal cortex. Arch Pathol Lab Med 1991; 115: 813–15.

21. Wieneke JA, Lack EE. The adrenal gland. In: Silverberg SG, DeLellis RA, Frable WJ, LiVolsi VA, Wick MR, eds. Silverberg's Principles and Practice of Surgical Pathology and Cytopathology, 4th edn. Churchill Livingstone Elsevier; 2006: 2169–209.

22. Lloyd RV, Douglas BR, Young WF. Adrenal gland. In: Endocrine Diseases. Atlas of Nontumour Pathology. King DW, ed. Washington, DC: American Registry of Pathology and the Armed Forces Institute of Pathology; 2002: 171–257.

23. Lack EE, Travis WD. Diagnostic problems in surgical pathology of the adrenal glands. Mod Pathol 1995; 8: 312–32.

24. Glicquel C, Leblond-Francillard M, Bertagna X et al. Clonal analysis of human adrenocortical carcinomas and secreting adenomas. Clin Endocrinol 1994; 40: 465–77.

25. Beuschlein F, Reincke M, Karl M et al. Clonal composition of human adrenocortical neoplasias. Cancer Res 1994; 54: 4927–32.

26. Diaz-Cano SJ, de Miguel M, Blanes A et al. Clonality as expression of distinctive cell kinetics patterns in nodular hyperplasias and adenomas of the adrenal cortex. Am J Pathol 2000; 156: 311–19.

27. Wajchenberg BL, Pereira MA, Medonca BB et al. Adrenocortical carcinoma. Clinical and laboratory observations. Cancer 2000; 88: 711–36.

28. Wooten MD, King DK. Adrenal cortical carcinoma. Epidemiology and treatment with mitotane and a review of the literature. Cancer 1993; 72: 3145–55.

29. Koch CA, Pacak K, Chrousos GP. Genetics of endocrine diseases. The molecular pathogenesis of hereditary and sporadic adrenocortical and adrenomedullary tumors. J Clin Endocrinol Metab 2002; 87: 5367–84.

30. Mayo-Smith WW, Lee MJ, McNicholas MM et al. Characterization of adrenal masses (<5 cm) by use of chemical shift MR imaging: observer performance versus quantitative measures. AJR 1995; 165: 91–5.

31. Tang CK, Gray GF. Adrenocortical Neoplasms. Prognosis and morphology. Urology 1975; 5: 691–5.

32. Aubert S, Wacrenier A, Leroy X et al. Weiss System Revisited. A clinicopathologic and immunohistochemical study of 49 adrenocortical tumors. Am J Surg Pathol 2002; 26: 1612–19.

33. Zhang PJ, Genega EM, Tomaszewski JE et al. The role of calretinin, inhibin, melan-A, BCL-2 And C-Kit in differentiating adrenal cortical and medullary tumors: an immunohistochemical study. Mod Pathol 2003; 16: 591–7.

34. Komminoth P, Roth J, Schröder S et al. Overlapping expression of immunohistochemical markers and synaptophysin mRNA in pheochromocytomas and adrenocortical carcinomas. Implications for the differential diagnosis of adrenal gland tumors. Lab Invest 1995; 72: 424–31.

35. Yang B, Ali SZ, Rosenthal DL. CD10 facilitates the diagnosis of metastatic renal cell carcinoma from primary adrenal cortical neoplasm in adrenal fine-needle aspiration. Diagn Cytopathol 2002; 27: 149–52.

36. Ribeiro RC, Sandrini F, Figueiredo B et al. An inherited p53 mutation that contributes in a tissue-specific manner to pediatric adrenal cortical carcinoma. PNAS 2001; 98: 9330–5.

37. Libé R, Bertherat J. Molecular genetics of adrenocortical tumours, from familial to sporadic diseases. Eur J Endocrinol 2005; 153: 477–87.

38. Ohgaki H, Kleihues P, Heitz PU. P53 mutations in sporadic adrenocortical tumors. Int J Cancer 1993; 54: 408–10.

39. Sidhu S, Martin E, Gicquel C et al. Mutation and methylation analysis of TP53 in adrenal carcinogenesis. Eur J Surg Oncol 2005; 31: 549–54.

40. Barzon L, Chilosi M, Fallo F. Molecular analysis of CDKN1C and TP53 in sporadic adrenal tumors. Eur J Endocrinol 2001; 145: 207–12.

41. Gicquel C, Bertagna X, Gaston V et al. Molecular markers and long-term recurrences in a large cohort of patients with sporadic adrenocortical tumors. Cancer Res 2001; 61: 6762–7.

42. Reincke M, Karl M, Travis WH et al. P53 mutations in human adrenocortical neoplasms: immunohistochemical and molecular studies. J Clin Endocrinol Metab 1994; 78: 790–4.

43. Zhi-HE G, Suvikki S, Jianqi L et al. Association of H19 promoter methylation with the expression of H19 and IGF-II genes in adrenocortical tumors. J Clin Endocrinol Metab 2002; 87: 1170–6.

44. Schmitt A, Saremaslani P, Schmid S et al. IGFII and MIB1 immunohistochemistry is helpful for the differentiation of benign from malignant adrenocortical tumors. Histopathology 2006; 49: 298–307.

45. Erickson LA, Jin L, Sebo TJ et al. Pathologic features and expression of insulin-like growth factor-2 in adrenocortical neoplasms. Endocr Pathol 2001; 12: 429–35.

46. Weiss LM. Comparable histologic study of 43 metastasizing and non metastasizing adrenocortical tumors. Am J Surg Pathol 1984; 8: 163–9.

47. Medeiros LJ, Weiss LM. New developments in the pathologic diagnosis of adrenal cortical neoplasms. A review. Am J Clin Pathol 1992; 97: 73–83.

48. Sasano H, Suzuki T, Moriya T. Discerning malignancy in resected adrenocortical neoplasms. Endocr Pathol 2001; 12: 397–406.

49. Wachenfeld C, Beuschlein F, Zwermann O et al. Discerning malignancy in adrenocortical tumors: are molecular markers useful? Eur J Endocrinol 2001; 145: 335–41.

50. Golblum JR, Randall S, Kaldjian EP et al. Immunohistochemical assessment of proliferative activity in adrenocortical neoplasms. Mod Pathol 1993; 6: 663–8.

51. McFarlane DA. Cancer of the adrenal cortex. The natural history, prognosis and treatment in a study of fifty-five cases. Ann R Coll Surg Engl 1958; 23: 155–86.

52. Sullivan M, Boileau M, Hodges CV. Adrenal cortical carcinoma. J Urol 1978; 120: 660–5.

53. Norton JA. Adrenal tumors. In: DeVita VT, Hellman S, Rosenberg SA, eds. Cancer Principles and Practice of Oncology, 5th edn. Philadelphia, PA: Lippincott-Raven; 1997.

54. Lin BTY, Bonsib SM, Mierau GW et al. Oncocytic adrenocortical neoplasms. A report of seven cases and review of the literature. Am J Surg Pathol 1998; 22: 603–14.

55. Hoang MP, Ayala AG, Albores-Saavedra J. Oncocytic adrenocortical carcinoma: a morphologic, immunohistochemical and ultrastructural study of four cases. Mod Pathol 2002; 15: 973–8.

56. Bisceglia M, Ludovico O, Di Mattia A et al. Adrenocortical oncocytic tumors: report of ten cases and review of the literature. Int J Surg Pathol 2004; 12: 231–43.

57. Lam KY, Lo CY. Adrenal lipomatous tumors: a 30 year clinicopathological experience at a single institution. J Clin Pathol 2001; 54: 707–12.

58. Bishop E, Eble JN, Cheng L et al. Adrenal myelolipomas show non-random x-chromosome inactivation in hemopoietic elements and fat: support for a clonal origin of myelolipomas. Am J Surg Pathol 2006; 30: 838–43.

59. Neumann HPH, Bausch B, McWhinney SR et al. Germ-line mutations in nonsyndromic pheochromocytoma. N Engl J Med 2002; 346: 1459–66.

60. Bravo EL. Evolving concepts in the pathophysiology, diagnosis and treatment of pheochromocytoma. Endocr Rev 1994; 15: 356–68.

61. Brink I, Hoegerle S, Klisch et al. Imaging of pheochromocytoma and paraganglioma. Fam Cancer 2005; 4: 61–8.

62. Medeiros LJ, Wolf BC, Balogh K et al. Adrenal pheochromocytoma: a clinicopathologic review of 60 cases. Hum Pathol 1985; 16: 580–9.

63. Linnoila RI, Keiser HR, Steinberg SM et al. Histopathology of benign versus malignant sympathoadrenal paragangliomas: clinicopathologic study of 120 cases including unusual histologic features. Hum Pathol 1990; 21: 1168–80.

64. Lamovec J, Frkovič-Grazio S, Bračko M et al. Nonsporadic cases and unusual morphological features in pheochromocytoma and paraganglioma. Arch Pathol Lab Med 1998; 122: 63–8.

65. Melicow MM. One hundred cases of pheochromocytoma (107 tumors) at the columbia-presbyterian medical center, 1926–1976: a clinicopathological study. Cancer 1977; 40: 1987–2004.

66. Proye C, Vix M, Goropoulos A et al. High incidence of malignant pheochromocytoma in a surgical unit. 26 cases out of 100 patients operated from 1971 to 1991. J Endocrinol Invest 1992; 15: 651–63.

67. Thompson LDR. Pheochromocytoma of the adrenal gland scaled score (PASS) to separate benign from malignant neoplasms. A clinicopathologic and immunophenotypic study of 100 cases. Am J Surg Pathol 2002; 26: 551–66.

68. Salmenkivi K, Heikkila P, Haglund C et al. Malignancy in pheochromocytomas. APMIS 2004; 112: 551–9.

69. Clarke MR, Weyant RJ, Watson CG et al. Prognostic markers in pheochromocytoma. Hum Pathol 1998; 29: 522–6.

70. Kumaki N, Kajiwara H, Kameyama K et al. Prediction of malignant behavior of pheochromocytomas and paragangliomas using immunohistochemical techniques. Endocr Pathol 2002; 13: 149–56.

71. Dannenberg H, Komminoth P, Dinjens WN et al. Molecular genetic alterations in adrenal and extra-adrenal pheochromocytomas and paragangliomas. Endocr Pathol 2003; 14: 329–50.

72. August C, August K, Schroeder S et al. CGH and CD44/MIB1 immunohistochemistry are helpful to distinguish metastasized from nonmetastasized sporadic pheochromocytomas. Mod Pathol 2004; 17: 1119–28.

73. Lameta S, Salmenkivi K, Pylkkanen L et al. Frequent loss of heterozygosity At 6q in pheochromocytoma. Hum Pathol 2006; 37: 749–54.

74. Lam KY, Lo CY. Composite pheochromocytoma–ganglioneuroma of the adrenal gland: an uncommon entity with distinctive clinicopathologic features. Endocr Pathol 1999; 10: 343–52.

75. Tischler AS. Divergent differentiation in neuroendocrine tumors of the adrenal gland. Semin Diagn Pathol 2000; 17: 120–6.

76. LaQuaglia MP. Surgical management of neuroblastoma. Semin Pediatr Surg 2001; 10: 132–9.

77. Hugosson C, Nyman R, Jorulf H et al. Imaging of abdominal neuroblastoma in children. Acta Radiol 1999; 40: 534–42.

78. Jakobs A, Delree M, Desprechins B et al. Consolidating the role of I-MIBG scintigraphy in childhood neuroblastoma: five years of clinical experience. Pediatr Radiol 1990; 20: 157–9.

79. Shimada H, Ambros IM, Dehner LP et al. The international neuroblastoma pathology classification (the shimada system). Cancer 1999; 86: 364–72.

80. Qualman SJ, Bowen J, Fitzgibbons PL et al. Protocol for the examination of specimens from patients with neuroblastoma and related neuroblastic tumors. Arch Pathol Lab Med 2005; 129: 874–81.

81. Foster DG. Adrenal cysts: review of the literature and report of a case. Arch Surg 1966; 92: 131–43.

82. Gaffey MJ, Mills SE, Fechner RE et al. Vascular adrenal cysts. A clinicopathologic and immunohistochemical study of endothelial and hemorrhagic (pseudocystic) variants. Am J Surg Pathol 1989; 13: 740–7.

83. Erickson LA, Lloyd RV, Hartman R et al. Cystic adrenal neoplasms. Cancer 2004; 101: 1537–44.

84. Raaf HN, Grant LD, Santoscoy C et al. Adenomatoid tumor of the adrenal gland: a report of four new cases and a review of the literature. Mod Pathol 1996; 9: 1046–51.

85. Isotalo PA, Keney GL, Sebo TJ et al. Adenomatoid tumor of the adrenal gland. A clinicopathologic study of five cases and review of literature. Am J Surg Pathol 2003; 27: 969–77.

86. Garg K, Lee P, Ro JY et al. Adenomatoid tumor of the adrenal gland: a clinicopathologic study of 3 cases. Ann Diagn Pathol 2005; 9: 11–15.

87. Lam KY, Lo CY. Metastatic tumours of the adrenal glands: a 30-year experience in a teaching hospital. Clin Endocrinol 2002; 56: 95–101.

88. Sagalowsky AI, Molberg K. Solitary metastasis of renal cell carcinoma to the controlateral adrenal gland 22 years after nephrectomy. Urol Online 1999; 54: 162.

Section 3

Pathology of tumors of the urinary bladder

Antonio Lopez-Beltran, Rodolfo Montironi, Alfredo Vidal-Jimenez, and Liang Cheng

Urinary bladder

An average of 260 000 new cases of urinary bladder cancer are diagnosed worldwide every year.[1,2] There are large regional variations with high incidence rates in the US, Western Europe, and Northern Africa, while the disease is relatively rare in Asia.[2] The incidence has been steadily increasing for decades but in some countries a decline has been observed recently.[1,2] Although bladder cancer is considered to be a man's disease and relatively rare among women, the number of women afflicted compares to that of cervical and ovarian cancer.[2] Bladder cancer presents mainly as non-muscle-invasive disease, which has a high recurrence of 50–70% with a low progression rate in 15–25% of the patients.[2,3] The high recurrence rate and the aggressiveness of these tumors have resulted in a close follow-up of patients. In the US, it was reported that Medicare expenditure in patients with cancer was the highest compared to other cancer disease. Bladder cancer incidence is nearly four times higher in men than in women and almost two times higher in Caucasians than in African Americans.[1] At histology, more than 90% of bladder cancer cases are urothelial (transitional cell) carcinoma (UC) and originate in the epithelial cells that line the bladder wall internally;[3] approximately 5% are squamous cell carcinoma, and less than 2% are adenocarcinoma; small cell carcinoma is less common.[3–5]

Etiology and epidemiology of bladder cancer

Bladder cancer is the sixth most common malignancy in developed countries.[1,2] It ranks as the fourth and ninth most frequently diagnosed cancer in men and women, respectively, in the United States.[1] It is estimated that about 67 160 cases will be newly diagnosed in the USA and 13 750 patients will die from disseminated carcinoma of urothelial mucosa in 2007.[1] Most bladder tumors in Western countries are urothelial carcinomas.[2–4] However, squamous cell carcinoma of the bladder is the predominant presentation in Middle Eastern countries.[4,6–8] Adenocarcinoma and small cell carcinoma of the bladder are less common.[5,8]

The etiology of bladder cancer is not fully understood, it has classically been associated with exogenous and environmental risk factors. The two best known risk factors for bladder cancer are smoking and occupational exposure.[2] Several potential carcinogens are inactive and need to be activated by enzymes controlled by genetic variables. For this reason the susceptibility to carcinogens differs among individuals and populations.

Smokers have between two and four times the risk of the general population, with heavy smokers being at five times the risk; the carcinogens involved are still unknown. It is estimated that 20 years of smoking are needed for the development of bladder cancer, and the risk directly correlates with the number of cigarettes consumed. The relative risk of smokers developing bladder cancer compared to non-smokers is 3:1, for previous smokers it is 1.9:1. The exact mechanism by which tobacco causes bladder cancer is not known, but urothelial carcinogens such as acrolein, 4-amino-biphenyl, arylamine, and oxygen free radicals have been implicated. Furthermore, increased duration, intensity of tobacco, and degree of inhalation significantly contribute to cancer development, while the beneficial effects of smoking cessation have been associated with an almost immediate decline in risk. With established tobacco-associated superficial UC of the bladder, continued smokers have worse recurrence-free survival than those who quit at the time of diagnosis.[2]

Occupational exposure to aniline dyes and aromatic amines such as 2-naphthylamine and benzidine has been implicated as the second most common risk factor for bladder cancer. Benzidine, the most carcinogenic aromatic amine, has been primarily used in dye production and as a hardener in the rubber industry. The degree of carcinogenesis due to occupational exposure varies with the degree of industrialization, but in heavily industrialized nations, occupational exposure may account for up to one fourth of all urothelial cancers. The latency period between exposure and tumor development is usually prolonged. Aromatic amines are now prohibited, but people exposed to chemical substances from the combustion of coal are also known to have an increased risk of bladder cancer. Occupational bladder cancer has also been observed in gas workers, painters, and hairdressers. Nutrition may also play a role as vitamin A supplement showed a reduced risk of bladder cancer, while fried food and fat caused a risk increase.[2] A high fluid intake was shown to reduce the risk of bladder cancer in one study but this remains controversial.[2] We have learned from Taiwan and Chile of an increased risk shown in populations using drinking water with a high content of arsenic, and these and other water contaminants are being actively investigated.[2]

Other factors implicated in the development and progression of bladder cancer include analgesic use, urinary tract infections including bacterial, parasitic, fungal, and viral infections, urinary lithiasis, pelvic radiation, and chemotherapeutic agents such as cyclophosphamide. Although caffeine ingestion has been implicated as a risk factor for bladder cancer, risk estimates for this association are decreased after controling for concomitant tobacco use. Similarly, saccharin-containing artificial sweeteners have been shown to induce bladder neoplasm in the rat model, but human epidemiologic studies have failed to establish this relationship. There is a relationship between the parasite bilharzia and squamous cell cancer in the bladder, more frequently seen in the Middle East.[2]

Clinical presentation and natural history of bladder cancer

Nearly 80% of patients who initially present with bladder UC have tumors confined to the mucosa or submucosa, so-called superficial 'non-muscle-invasive' bladder cancers, more appropriately reported as stage Ta/T1 urothelial tumors.[2,3,9–14] Superficial bladder tumors represent a heterogeneous group of cancers that include those that are (1) papillary in nature and limited to the mucosa (stage Ta), and (2) those that are invasive into the lamina propria or submucosa when the muscularis mucosae is present (stage T1). Although flat carcinomas in situ (Tis) have been included historically as part of the group of superficial bladder cancer, this practice has been discouraged by most authorities including the World Health Organization (WHO).[15,16] The remainder of bladder cancer patients present initially with bladder tumors invading the muscularis propria of the bladder or beyond (stage T2–T4).[17]

Approximately three-quarters of patients with bladder cancer present with painless, intermittent hematuria.[2] It is estimated that approximately 20% of patients being evaluated for gross hematuria will subsequently be diagnosed with bladder cancer. Similarly, of patients presenting with microscopic hematuria, up to 10% will be diagnosed with bladder cancer. Microscopic hematuria in patients with bladder cancer tends to be unpredictable and inconsistent; therefore a single negative urinalysis does not exclude the possibility of cancer.[2] One-quarter of patients with bladder cancer will present with irritative voiding symptoms of urgency, frequency, and dysuria, symptoms frequently misinterpreted as signs of a urinary tract infection but that may signify either trigone involvement with tumor or the presence of carcinoma in situ.[18,19]

The initial evaluation and management for patients with suspected bladder cancer involves cystoscopic evaluation of the bladder, transurethral resection (TUR) of visible tumor, and assessment of the appearance of the uninvolved bladder and prostatic urethra, which may be indicated when visible abnormalities of the prostatic urothelium exist.[2] Small lesions and flat lesions worrisome for carcinoma in situ (CIS) can be sampled with cold-cup biopsy forceps while larger lesions should be completely resected.[14] In addition, during TUR, attempts should be made to obtain muscularis propria. The presence of smooth muscle in the pathologic specimen is an important indicator for an adequately performed resection.[4,20] It is clear that up to 4% of patients with superficial bladder cancer are at risk for synchronous and metachronous upper urinary tract tumors.[21] Patients with a history of CIS, tumors adjacent to the ureteral orifices, or those with persistently unexplained positive cytologies might be at increased risk of an upper tract tumor or prostatic urethral tumor involvement.[21]

The natural history of bladder cancer is difficult to predict due to biological heterogeneity; features that characterize superficial (stage Ta or T1) bladder cancer are disease recurrence and progression.[2,17,22] The risks for both recurrence and tumor progression are related to multiple histopathologic factors including grade, depth of invasion, multiplicity, tumor size, tumor morphology, presence or absence of vascular or lymphatic invasion, and the presence or absence of CIS.[23,24] Although these conventional measures provide some degree of prognostic information, they fail to clearly evaluate each individual tumor's malignant potential. These shortcomings with traditional clinical and histopathologic features have therefore led to significant efforts to better define a tumor's true biological potential on a molecular level.[3,4,25–29] Unfortunately, the molecular markers do not have significant clinical application at the current time.

Nearly 60 to 90% of patients with superficial disease will have a tumor recurrence if treated by TUR alone. A retrospective analysis of 176 patients from Sweden with superficial TCC, who were followed until death or for at least 20 years (with no adjuvant therapy), provides some insight into the importance and natural history of this disease left untreated.[24] An overall recurrence rate of 80% was reported with 22% of patients dying from the disease if followed long enough. In this study, death was directly related to tumor grade, number of tumors, and volume of recurrences.[24]

Pathology of bladder cancer

Approximately 80% of patients with primary urothelial carcinoma will display a relatively indolent, low-grade tumor confined to the superficial mucosa.[2,3] Despite the relatively indolent nature of superficial urothelial tumor, the recurrence rate can be as high as 70%, thus necessitating long-term follow-up.[2,3,30–32] In addition, about one-third of recurrent superficial tumors may eventually progress to a higher grade and/or stage.[10] Three basic diagnostic categories are identified in the urinary bladder on the basis of the pattern of growth of the urothelial tumors (flat, papillary non-invasive, or infiltrative).[2,3] Their clinical behaviors are also related to the degree of architectural, cytologic, and molecular alterations of the urothelium.[13,18,19] Several classifications have been reported in the literature, and current genetic data suggest two major pathways that correspond to morphologically defined entities.[2,3,16,33,34] The genetically stable category includes low-grade non-invasive papillary tumors (pTa, G1 and G2 or papillary urothelial neoplasm of low malignant potential (PUNLMP) and LG).[4] The genetically unstable category contains high-grade non-invasive (including pTa G3 or HG and CIS) and infiltrating carcinomas (stage pT1–4).[4] Non-invasive low-grade bladder neoplasms have fewer genomic alterations and are therefore viewed as genetically stable. Invasive tumors appear to be genetically unstable and have more chromosomal aberrations. The potential value for this classification also depends on accurate diagnosis and consistent separation of pTa from pT1 tumors.[12,14,35–39] Recognition of early invasion (stage pT1) in urothelial neoplasia is one of the most challenging areas in bladder pathology, and reproducibility between pathologists is a major issue.[14,39] This fact, together with the proposal by some urologists to treat early invasive tumors more aggressively, makes the accurate diagnosis of pT1 tumors even more relevant in clinical practice.[40,41]

Flat intra-epithelial lesions

The urothelium is composed of basal, intermediate, and superficial cells without cytologic atypia (Figure 3.1). The number of cell layers may vary (usually less than seven) due to tangential sectioning.[41] Malignancy-associated cellular change (MACC) is a recently introduced concept, encompassing urothelial abnormalities of bladders harboring neoplastic lesions that are not detectable by routine light microscopy. However, MACC is detectable when chromatin analysis or genetic studies are performed. Most reports show chromosome 9 alterations in MACC, similar to those in the coexistent carcinoma. The clinical relevance of MACC remains to be established but could be important at time of evaluation of the urothelial status after surgery[13] (Table 3.1).
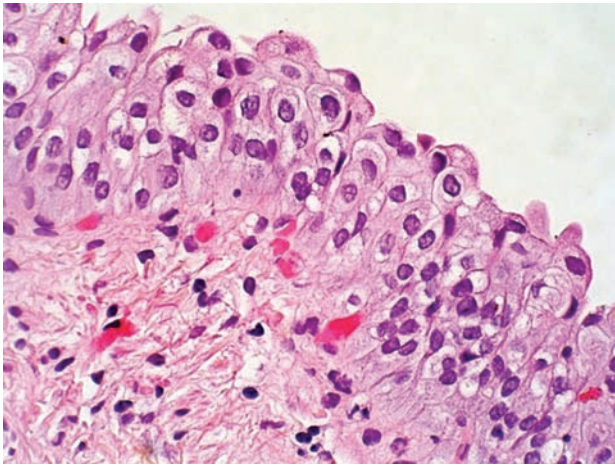
Figure 3.1
Normal bladder urothelium.

Figure 3.2
Flat urothelial hyperplasia.

Table 3.1 WHO 2004 classification of non-invasive urothelial neoplasia[16]

Hyperplasia (flat and papillary)
Dysplasia
Urothelial papilloma
Urothelial papilloma, inverted type
Non-invasive papillary urothelial neoplasia of low malignant potential
Non-invasive urothelial carcinoma, low-grade
Non-invasive urothelial carcinoma, high-grade
Carcinoma in situ

Figure 3.3
Urothelial dysplasia.

Urothelial hyperplasia

Urothelial hyperplasia is characterized by markedly thickened mucosa without cytological atypia[41,42] (Figure 3.2). It may be seen adjacent to low-grade urothelial papillary tumors. Within the spectrum of hyperplasia, a papillary architecture may be present, and most of these patients have concomitant papillary tumors. When seen isolated (primary hyperplasia), there is no evidence suggesting that it has a premalignant potential.[42] However, molecular analyses have shown that it may be clonally related to the papillary tumors in bladder cancer patients.[42]

Urothelial dysplasia

Dysplasia is an intra-urothelial lesion with cytologic and architectural changes that are believed to be preneoplastic but which fall short of CIS[13,14] (Figure 3.3). The urothelium of dysplasia typically shows cohesive cells characterized by nuclear/nucleolar changes that include irregular nuclear crowding and nuclear hyperchromasia. Nucleoli may be prominent and mitotic figures, when present, are generally basally located. The umbrella cells are usually present. Most cellular abnormalities in dysplasia are restricted to the basal and intermediate cell layers.[13,18,43] Nuclear and architectural features are most useful in distinguishing reactive urothelial atypia and dysplasia.
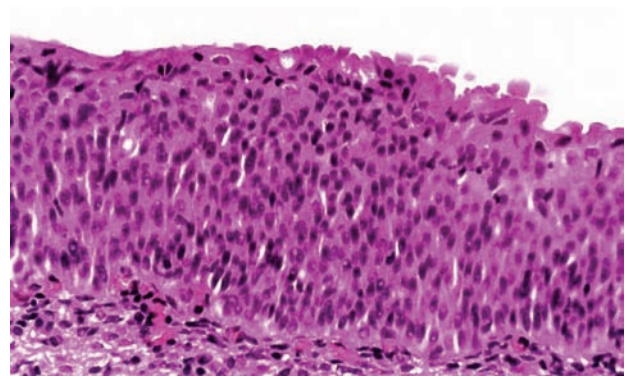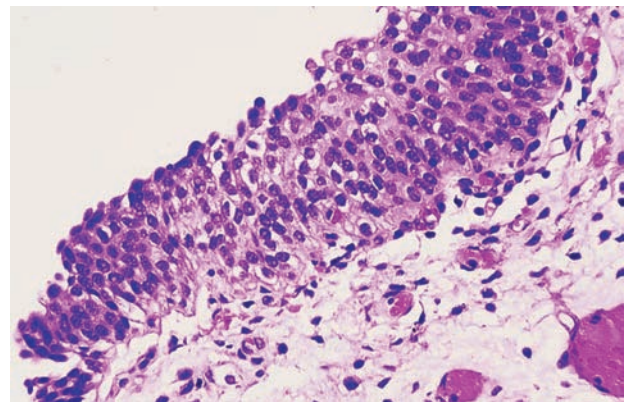
Occasionally, there may be an increased number of cell layers and dysplasia. Cytokeratin 20 may be of value in its recognition.[44] Alterations of p53 and allelic losses, particularly in chromosome 9, have been demonstrated to occur in dysplasia.[43] Dysplasia is most relevant in non-invasive papillary neoplasms, where its presence indicates urothelial instability and is a marker for recurrence or progression. De novo (primary) dysplasia progresses to bladder neoplasia in about 15–19% of cases.[13] The use of the term atypia as synonymous with urothelial dysplasia is discouraged. Due to inherent inter- and intra-observer variability, grading of urothelial dysplasia is not recommended.

Urothelial carcinoma in situ

CIS is a non-papillary flat lesion in which the surface epithelium contains cells that are cytologically malignant and the morphologic diagnosis of CIS requires severe cytologic atypia[19,45] (Figure 3.4). Full thickness change is not essential, although it is usually present.[13,41,46,47] Prominent disorganization of cells is characteristic, with loss of cellular polarity and cohesiveness. The tumor cells tend to be large and pleomorphic, with moderate to abundant cytoplasm, although they are sometimes small with a high nuclear to cytoplasmic ratio. The chromatin tends to be coarse and clumped. Nucleoli are usually large and prominent in at least some of the cells, and may

be multiple. Mitotic figures that may be atypical are also seen in the uppermost layers of the urothelium. Superficial (umbrella) cells may be present in CIS.

Some growth patterns and/or morphologic variants of CIS have been recognized in recent years.[47] Individual neoplastic cells may be seen scattered amidst normal urothelium (pagetoid pattern) (Figure 3.5). Loss of intercellular cohesion of CIS may result in the so-called 'denuding cystitis' or in residual neoplastic cells attached to the surface ('clinging' pattern). Small and large cell variants have been described. CIS cells may involve von Brunn's nests and cystitis cystica.[13,46–48] Cytokeratin 20 is abnormally expressed in CIS. Abnormal expression of p53 (Figure 3.6) and RB (retinoblastoma) protein may correlate with progression of CIS or response to BCG (bacilus Calmette-Guerin) therapy. The nuclear matrix protein NMP22 is present in CIS.

Cytogenetically CIS shows close similarities to invasive tumors. Primary (de novo) CIS accounts for 1–3% of urothelial neoplasms and is most commonly seen in the bladder. Approximately 15% of patients with CIS of the bladder will have prostatic urethral involvement and, occasionally, a recurrent tumor is found in the urethral stump after cystectomy. The distal ureter is involved in 6–60%, the prostatic urethra in 20–67%, and the prostate ducts and acini in up to 40%. Primary CIS is less likely to progress to invasive disease than secondary CIS.[19,45] Approximately 45–65% of patients with CIS and concomitant invasive tumors will die of the disease, as compared to
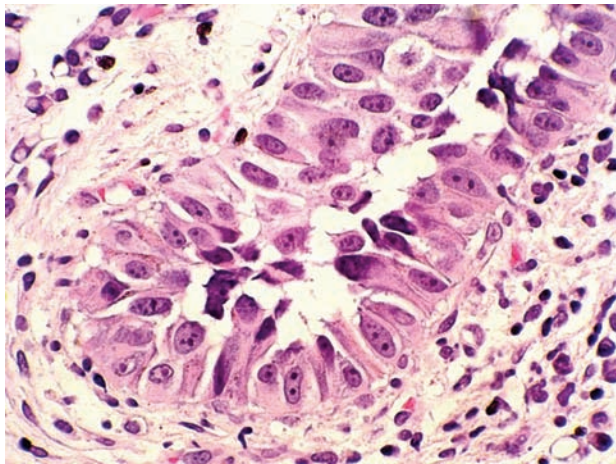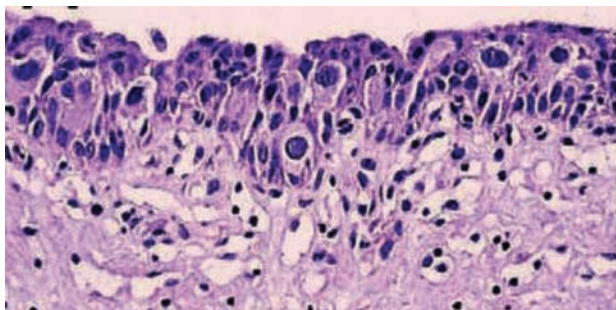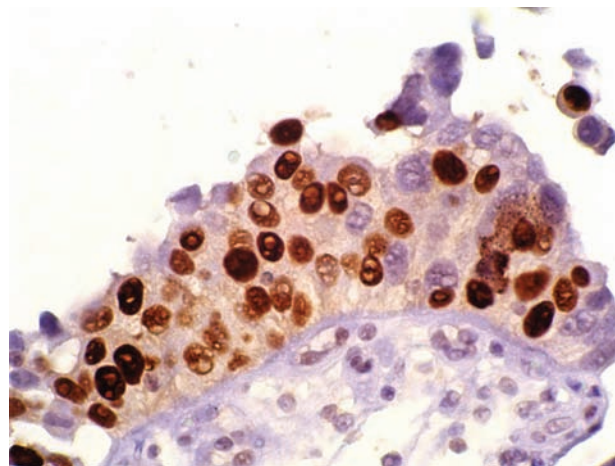

Figure 3.6
Bladder carcinoma in situ showing extensive p53 accumulation.

7–15% of patients with primary CIS with or without concomitant non-invasive papillary tumors. CIS with aneuploid karyotypes appears to be at high risk of progression.

Figure 3.4
Bladder carcinoma in situ.

Figure 3.5
Pagetoid carcinoma in situ.

Classification of non-invasive (stage Ta) papillary urothelial neoplasia

The topic of the best contemporary classification and grading system of the non-invasive papillary neoplasia has been debated and should still be considered unsettled.[2,3,15,27,30,41,49–76] From the practical point of view, the use of both the 1973 and 2004 WHO classifications (former 1998 ISUP/WHO) have been recommended until the latter is sufficiently validated[3,20] (Table 3.2). Bladder cancer may develop via a variety of pathways. Most tumors have a papillary configuration at diagnosis. Additional genetic changes may induce the development of higher-grade papillary lesions. The 2004 WHO classification recommends stratifying patients according to stage, that is non-invasive papillary (stage Ta) and invasive (stage T1–T4).[3] Clearly, urothelial carcinoma represents a heterogeneous entity with significant malignant potential. The most important predictors of clinical course in non-invasive urothelial tumors are pathologic grade, multiplicity, early recurrence, and tumor size, but the presence of dysplasia and CIS in the adjacent urothelium can be relevant as well (Table 3.3).

Several classifications have been reported in the literature, and current genetic data suggest two major pathways that correspond to morphologically defined entities. The genetically stable category includes low-grade (grade 1 and some grade 2, 1973 WHO scheme) non-invasive papillary tumors.[15,66] The genetically unstable category contains high-grade (some grade 2 and all grade 3, 1973 WHO scheme) non-invasive and CIS, and invasively growing carcinomas (stage T1–4). Non-invasive low-grade bladder neoplasms have only a few genomic alterations and are therefore viewed as genetically stable. Some classifications and grading schemes of the urothelial neoplasms have been reported in the literature. The recent 2004 WHO (former ISUP/WHO 1998) classification reflects work in progress.[14,41] The 1973 WHO classification is preferred by some authors as it allows valid comparison of results between different clinical centers.

Table 3.2 Histologic type of tumors of the urinary bladder (WHO, 2004)[16]

Urothelial neoplasia
  Benign
    Urothelial papilloma
    Inverted papilloma
  Papillary urothelial neoplasia of low malignant potential
  Malignant papillary
    Papillary carcinoma, low grade
    Papillary carcinoma, high grade
    Papillary carcinoma with squamous or glandular differentiation
  Malignant non-papillary
    Flat carcinoma in situ
    Invasive carcinoma
    Variants of invasive carcinoma
      Nested pattern
      Small tubular pattern
      Microcystic pattern
      Inverted pattern
      With squamous differentiation
      With glandular differentiation
      Micropapillary
      Sarcomatoid carcinoma
      Clear cell urothelial carcinoma
      Plasmocytoid
      With syncytiotrophoblasts
      With unusual stromal reactions
        Pseudosarcomatous stroma
        Stromal osseous or cartilaginous metaplasia
        Osteoclast-type giant cells
        With prominent lymphoid infiltrate
Squamous cell carcinoma
  Usual type
  Variant
  Verrucous
  Basaloid
  With sarcomatoid features
Adenocarcinoma (from bladder mucosa, urachal, with extrophy)
  Usual intestinal type
  Mucinous (including colloid)
  Signet-ring cell
  Clear cell
Hepatoid
Mixture of above patterns
Adenocarcinoma NOS (not otherwise specified)

Tumors of mixed cell types
Undifferentiated carcinomas*
  Small cell carcinoma
  Large cell neuroendocrine carcinoma
  Lymphoepithelioma-like carcinoma
Giant cell carcinoma
Undifferentiated carcinoma NOS
Metastatic carcinoma

*Refers to tumors that are undifferentiated by light microscopy.

The standard 1973 WHO classification and grading of bladder tumors is a robust, clinically proven, widely used, time-tested, and reasonably reproducible method for pathologic reporting, and therefore is still recommended. Some controversies followed the introduction of 1998 WHO/ISUP classification of bladder tumors, mainly because of lack of validation, reproducibility, and translation studies. In particular, there is a poor interobserver agreement for PUNLMP and low-grade urothelial carcinoma ($\kappa = 0.12$ to 0.50).

After structured training for the new 1998 WHO/ISUP grading system, Murphy et al[60,61] concluded that neither refinements of morphologic criteria nor additional education would significantly decrease interpretive discrepancy in the grading of urothelial carcinoma. In a recent study, Bol et al[35] found that agreement among three experienced pathologists on the diagnosis of papillary urothelial neoplasms of low malignant potential was 0%.[2,3,15,27,30,41,49,50–76]

The natural history shows that bladder cancer is actually two diseases. The first is low-grade, papillary, non-invasive urothelial tumors (PUNLMP and low-grade), previously classified as grade 1, and characterized by genetic stability with common chromosome 9 alterations and frequent FGFR3 mutations.[66] These tumors have a high propensity to recur but rarely invade or metastasize. The second type of bladder cancer is the high-grade lesion that originates as urothelial dysplasia and begins as CIS or high-grade, non-invasive, papillary carcinoma (grade 3 and some grade 2, 1973 WHO scheme). This has common alterations at the TP53 and RB tumor suppressor genes. Both types of neoplasm can develop in the same patient, either simultaneously or sequentially. Non-invasive papillary urothelial lesions, according to the 2004 WHO classification, distinguish urothelial papilloma and inverted papilloma, the controversial lesion PUNLMP, as well as non-invasive, low- and high-grade urothelial carcinoma. The main clinico-pathologic features of these categories follow.

Benign epithelial tumors

Urothelial papilloma and diffuse papillomatosis

Urothelial papilloma is a benign exophytic neoplasia composed of a delicate fibrovascular core covered by normal looking urothelium (Figure 3.7). The superficial cells are often prominent. Mitoses are absent to rare and, if present, are located in the basal cell layer. The stroma may show edema and/or inflammatory cells.[15,56] Papillomas are diploid with low proliferation, uncommon p53 expression, and frequent FGFR3 (75%) mutation.[77] Cytokeratin 20 expression is limited to the superficial (umbrella) cells as is usual in normal urothelium. The incidence is below 1% of all bladder tumors and the male:female ratio is 1.9:1. Hematuria is common. Most papillomas are single and occur in younger patients (mean age 46 years), close to the ureteric orifices in most cases. Urothelial papilloma may recur; however, it does not progress.[56] Diffuse papillomatosis applies when the mucosa is extensively involved by small delicate papillary processes creating a velvety cystoscopic appearance.

Inverted papilloma

Inverted papilloma applies to a benign urothelial tumor that has an inverted growth pattern with normal to minimal cytologic atypia of the cells[78–81] (Figure 3.8). Most cases are solitary nodular or sessile lesions, smaller than 3 cm, and arise in the bladder trigone, but can also be found along the urinary tract. At histology, the inverted papilloma has a smooth surface covered by normal urothelium and endophytic cords of urothelial cells invaginating extensively from the surface urothelium into the subjacent lamina propria, but not into the muscular bladder wall.[78–81] Trabecular and glandular variants
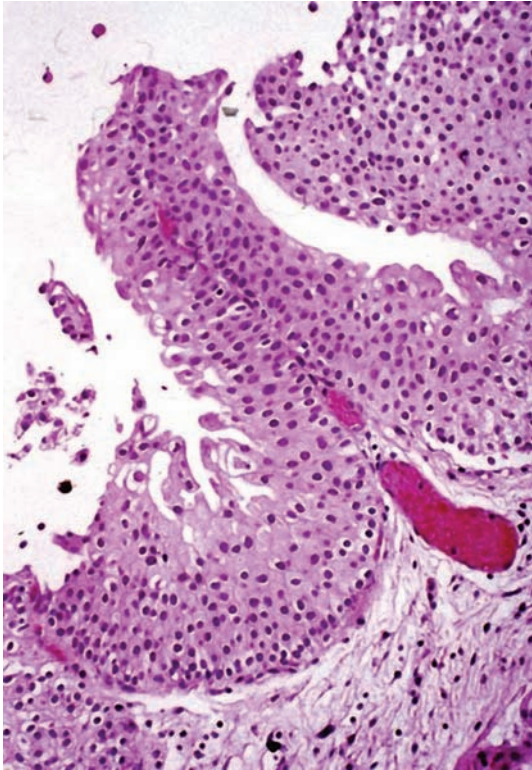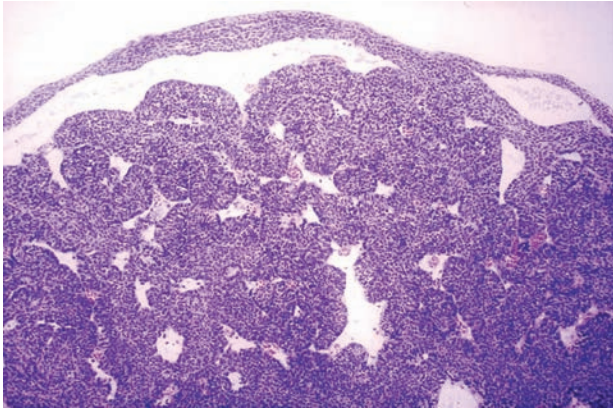
Figure 3.7
Urothelial papilloma.

Figure 3.8
Inverted papilloma.

have been described. Foci of non-keratinizing squamous metaplasia and neuroendocrine differentiation have been reported. Focal minor cytologic atypia may be present but mitotic figures are not seen or are very rare. Inverted papilloma may coexist with carcinoma. The male:female ratio is 4–5:1. The age of the patients ranges from 10 to 94 years. Hematuria or obstructive symptoms are common and less than 1% of cases recur. Recent studies indicate that inverted papilloma is a monoclonal process; however, the low incidence of LOH supports the view that inverted papilloma in urinary bladder is a benign neoplasm with molecular genetic abnormalities different from those of clirothelial carcinoma. It seems that inverted papilloma diagnosed according to strictly defined criteria is a benign urothelial neoplasm, not related to urothelial carcinoma.[78–81]

Other benign epithelial tumors arising in the urinary bladder

Squamous cell papilloma is a rare benign neoplasm, presumably the squamous counterpart of urothelial cell papilloma. It seems to be unrelated to human papillomavirus infection. At histology it is composed of papillary cores with overlying benign squamous epithelium and is different to condyloma acuminatum that rarely affects the bladder and is related to 'low risk' papillomavirus infection.[79,82]

Villous adenoma is an uncommon benign glandular epithelial neoplasm with exophytic growth that is often associated with urachal adenocarcinoma, but that may be seen elsewhere in the bladder. Histologically it is identical to villous adenoma of the colon, showing columnar mucinous cells and goblet cells lining delicate fibrovascular stalks with nuclear stratification, crowding, and hyperchromasia. The differential diagnosis includes adenocarcinoma arising in the bladder.[79]

Papillary urothelial neoplasm of low malignant potential

PUNLMP is a controversial lesion defined as a non-invasive papillary urothelial tumor which resembles the exophytic urothelial papilloma but shows increased cellularity exceeding the thickness of normal urothelium[3,15,49] (Figure 3.9). At cystoscopy, most cases are solitary, 1–2 cm in diameter, and located in the lateral or posterior wall, close to the ureteric orifices. The papillae are slender without fusion and lined by multilayered urothelium with minimal to absent cytologic atypia. The cell polarity is preserved with minimal variation in the architecture. The nuclei are slightly enlarged and the superficial cell layer is preserved. Mitoses are rare and have a basal location. These tumors are considered non-invasive grade 1 papillary urothelial carcinoma in the 1973 WHO scheme. Most are diploid with a low proliferation rate, but show frequent FGFR3 mutation and allelic loss in 80% and 81% of cases, respectively. Gross or microscopic hematuria is frequent. The male:female ratio is 5:1 and the mean age at diagnosis is 65 years (range 29–94 years). Mean reported tumor recurrence, stage progression, and tumor-related mortality occur in approximately 35%, 4%, and 2% of patients, respectively. In some series, stage progression can be as high as 8%[2,3,53,54] (Table 3.3).
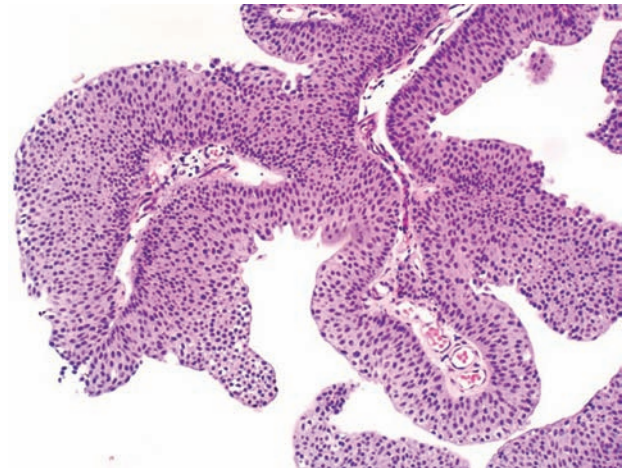

Figure 3.9
Papillary urothelial neoplasia of low malignant potential.

Table 3.3 Follow-up studies on papillary urothelial neoplasia of low malignant potential and urothelial carcinoma, low grade

	Tumor recurrence*	Stage progression*	Tumor-related mortality*
PUNLMP	35.58 (25–47)	3.72 (0–8)	1.23 (0–3.90)
Low-grade carcinoma	49.99 (30.49–76.70)	9.65 (3.53–13.00)	4.42 (3.54–5.30)

PUNLMP: papillary urothelial neoplasia of low malignant potential.
*Mean percentage (range).

Non-invasive papillary urothelial carcinoma, low- and high-grade

This is a low-grade neoplasm of urothelium lining papillary fronds which shows recognizable variations in architecture and cytology[2,3,15,53,54] (Figure 3.10). The tumor shows slender papillae with frequent branching, minimal fusion, and variations in nuclear polarity, size, shape, and chromatin pattern and with the presence of nucleoli. Mitoses may occur at any level in those cases of low grade (Table 3.4). These cases are considered as grade 1 or grade 2 in the 1973 WHO classification scheme. Altered expression of cytokeratin 20, CD44, p53, and p63 is frequent; some tumors are diploid. FGFR3 mutations are seen at about the same frequency as that for PUNLMP.[30] The male:female ratio is 2.9:1 and the mean age is 70 years (range 28–90 years). Most patients present with hematuria and have a single tumor in the posterior or lateral wall; however, 22% of them have two or more tumors. Tumor recurrence, stage progression, and tumor-related mortality are approximately 50%, 10%, and 5%, respectively, but stage progression can be as high as 13% in some series (Table 3.3).

In high-grade tumors (all grade 3 and some grade 2, 1973 WHO scheme) the urothelium lining papillary fronds shows a predominant disorder with moderate-to-marked architectural and cytologic atypia, with the papillae frequently fused and variations in architectural and cytologic features that are easily recognizable even at scanning power[15] (Figure 3.11). The nuclei are often pleomorphic with prominent nucleoli and altered polarity. Mitoses are frequent. The thickness of the urothelium varies considerably. Carcinoma in situ is frequent in the adjacent mucosa. Changes in cytokeratin 20, p53, and p63 expression and aneuploidy are more frequent than in previous categories. Molecular alterations in these tumors show a frequency of p53, HER2, or EGFR overexpression and p21Waf1 or p27kip1 loss comparable to that seen in invasive cancers. Genetically, high-grade non-invasive lesions (pTa G3) resemble invasively growing tumors. A comparative genomic hybridization-based study showed deletions at 2q, 5q, 10q, and 18q as well as gains at 5p and 20q. Hematuria is common and the endoscopic appearance varies from papillary to nodular/solid single or multiple tumors. Progression in terms of stage and death due to disease can be observed in as many as 65% of patients.[4]

Bladder cancer staging

Ta tumors account for approximately 70% of superficial transitional cell carcinoma (TCC). These tumors are composed of branching fibrovascular cores with greater than eight cell layers that display
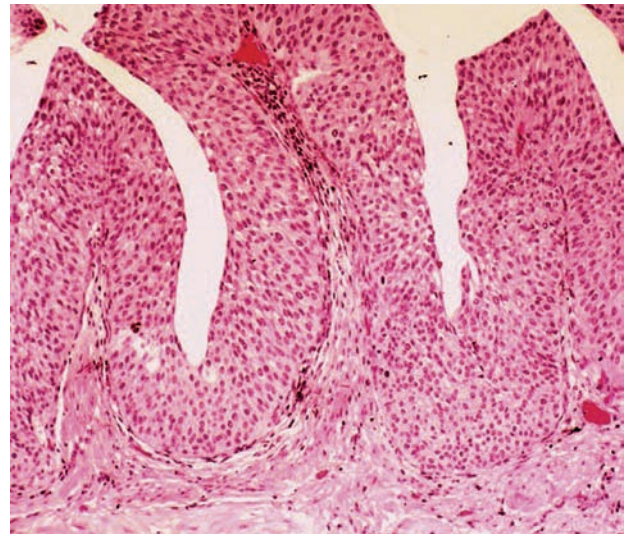

Figure 3.10
Non-invasive papillary urothelial carcinoma, low-grade.

features of cytologic atypia and architectural distortion. This arrangement provides their morphologic papillary appearance. In general, Ta tumors are low-grade cancers. T1 tumors by definition invade the submucosa (also called lamina propria) and account for approximately 30% of all non-invasive bladder tumors. T1 lesions may have either a papillary or broad-based appearance, and are generally of higher grade than Ta tumors[14] (Figure 3.12). T2–T3 tumors, by definition, are muscle-invasive tumors or readily invade the perivesical fat; higher lesions (stage T4) invade adjacent organs[14] (Figure 3.13).

Although not addressed in the current TNM system,[83] several studies have proposed further substaging of T1 lesions.[12,14,84–101] There are data to suggest a significant difference in prognosis and survival based upon the depth of submucosal invasion, with a worse prognosis associated with increasing submucosal invasion. A T1 substaging has been based on the following system: T1A, invasion of connective tissue superficial to the level of the muscularis mucosae; T1B, invasion to the level of the muscularis mucosae; and T1C, invasion through the level of the muscularis mucosae but superficial to the muscularis propria (detrusor muscle).[12,14,84–101] Opponents to this subclassification argue that it is often difficult to accurately assess the TUR tissue for the presence and actual depth of invasion because of orientation and artifactual changes. Similarly, it is argued that muscularis mucosae cannot be consistently identified with certainty in all biopsy specimens.

Table 3.4 Histologic characteristics of non-invasive papillary urothelial tumors of the bladder according to the WHO, 2004[16]

|	*Papilloma*	*Papillary neoplasm of low malignant potential*	*Low-grade papillary carcinoma*	*High-grade papillary carcinoma*
Architectural features				
Papillae	Delicate	Delicate Occasionally fused Not branching	Fused, branching	Fused, branching
Organization of cells	Identical to normal urothelium	Ordered. Polarity identical to normal urothelium. Any thickness. Cohesive	Predominantly ordered, minimal crowding and minimal loss of polarity. Any thickness. Cohesive	Predominantly disordered with frequent loss of polarity. Variable thickness. Discohesive
Cytologic features				
Nuclear size	Identical to normal urothelium	May be enlarged but uniform	Enlarged with variation in size	Enlarged with variation in size readily visible
Nuclear shape	Identical to normal urothelium	Elongated, round-oval, uniform	Round-oval. Slight variation in shape and contour	Moderate-marked pleomorphism
Nuclear chromatin	Fine	Fine	Mild variation	Moderate-marked variation. Hyperchromasia
Nucleoli	Absent	Absent to inconspicuous	Usually inconspicuous	Multiple prominent nucleoli may be present
Mitoses	Absent	Rare, basal	Occasionally at any level	Usually frequent, at any level
Umbrella cells	Uniformly present	Present	Usually present	Usually absent
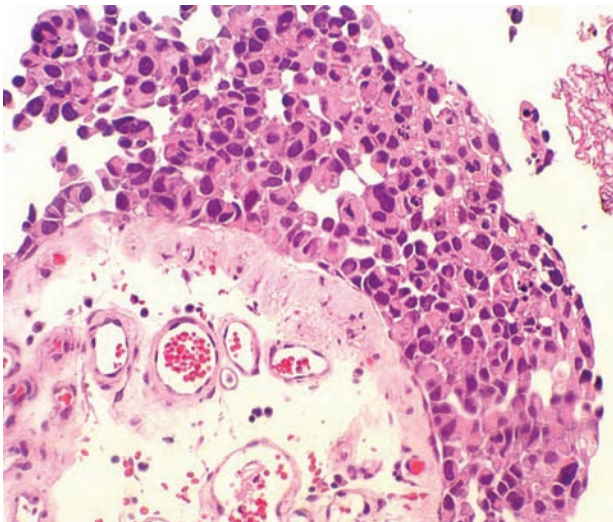
Figure 3.11
Non-invasive papillary urothelial carcinoma, high-grade.

Figure 3.12
Gross appearance of urothelial carcinoma in the bladder neck.

In 1999, Cheng et al proposed a novel system of substaging pT1 tumors based on the micrometric measurement of the depth of invasion of tumor into the subepithelial connective tissue.[12] They studied a series of 55 patients with stage pT1 urothelial carcinomas diagnosed on transurethral resection of bladder tumor (TURBT) specimens and eventually treated by cystectomy. By using an ocular micrometer to measure the depth of invasion from the mucosal basement membrane, the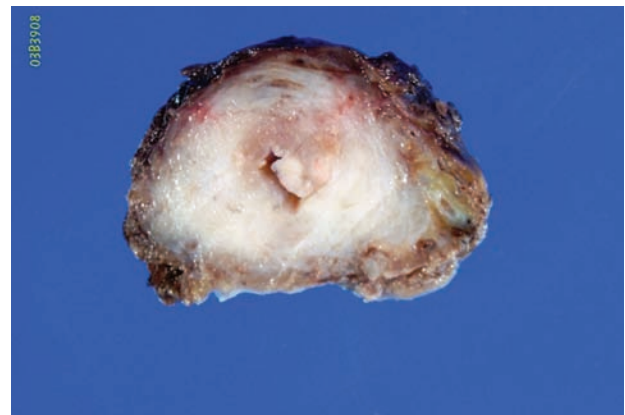y found a significant correlation between depth of invasion in the TURBT specimen and final pathologic stage on cystectomy.[12] A 1.5 mm depth of invasion predicted advanced stage of disease at cystectomy with a sensitivity of 81%, a specificity of 83%, and positive and negative predictive values of 95% and 56%, respectively. They further applied the same criteria to a group of 83 consecutive patients diagnosed with pT1 bladder cancer and found a 5-year progression-free survival of 67% in patients with a depth of tumor invasion of >1.5 mm, compared to 93% for those tumors with a depth of invasion <1.5%.[12,14]
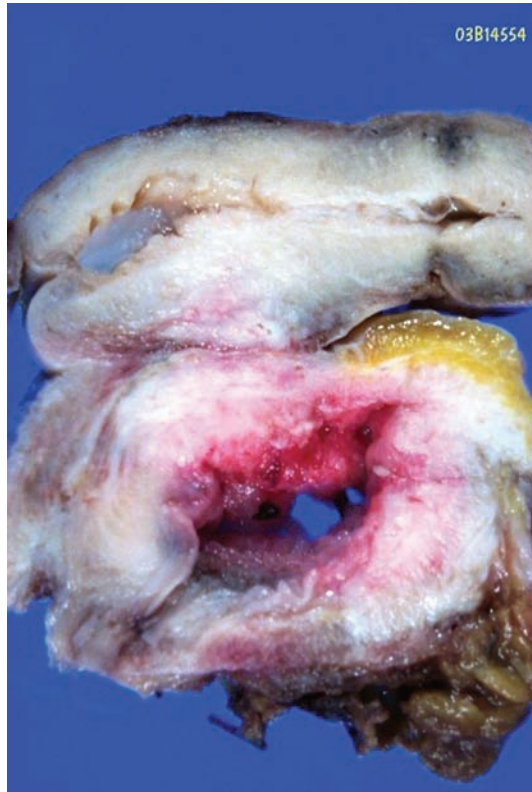
Figure 3.13
Urothelial carcinoma in perivesical fat and the uterus (stage pT4).

Figure 3.14
Invasive urothelial carcinoma in lamina propria, stage pT1.
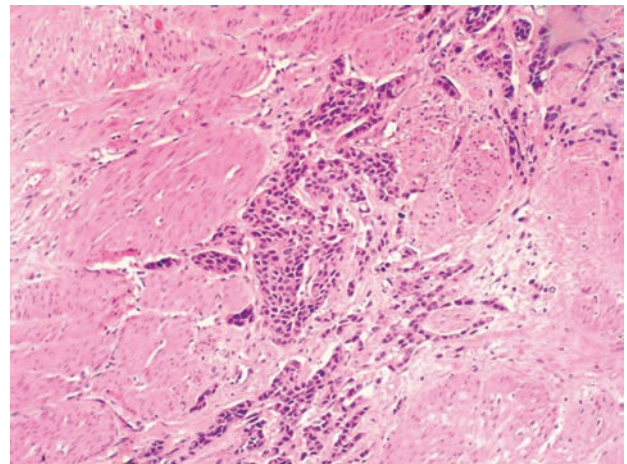
Figure 3.15
Invasive urothelial carcinoma in muscularis propria, stage pT2.

Invasive bladder carcinoma

Grading of infiltrating urothelial carcinoma (stage T1–T4)

Infiltrating urothelial carcinoma is defined as a urothelial tumor that invades beyond the basement membrane.[4] Infiltrative carcinomas grossly span a range of morphology including papillary, polypoid, nodular, solid, ulcerative, or transmural diffuse. They may be solitary or multifocal. The histology of infiltrating urothelial carcinomas is variable and includes pT1–T4 tumors. Most pT1 cancers are papillary and low- or high-grade (Figure 3.14), whereas most pT2–T4 carcinomas are infiltrating and high-grade, and therefore will be discussed separately (Figure 3.15). Infiltrating urothelial carcinomas are classified as low- or high-grade according to the new 2004 WHO classification, depending upon the degree of nuclear anaplasia and architectural abnormalities.[85,99,102–105]

Morphologic characteristics of bladder carcinoma with early stromal invasion (stage T1)

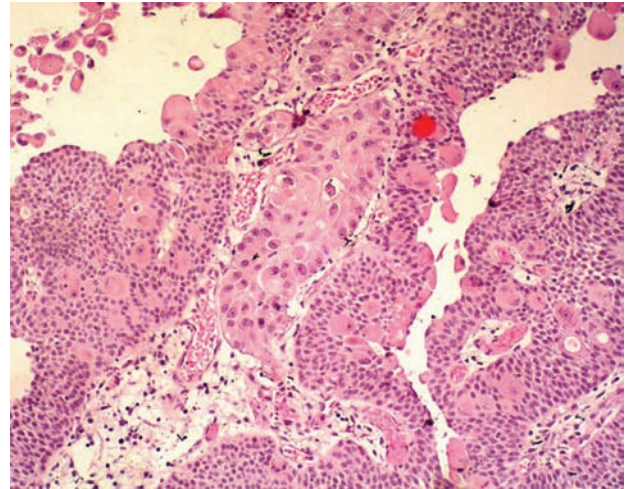Stage is the single most important prognostic indicator in urothelial carcinoma. Infiltrating urothelial carcinoma is defined by the WHO as a urothelial tumor that invades beyond the basement membrane.[4] The 2002 TNM (tumor, lymph nodes, and metastasis) staging system defines pT1 tumors of the bladder as those invading the lamina propria, but not the muscularis propria. Although pT1 tumors have a less favorable prognosis than pTa (non-invasive) tumors, clinically they are both usually lumped together under the term 'superficial' bladder tumors, a practice no longer recommended.[14] Muscularis mucosae is often present in the lamina propria, and consists of thin and wavy fascicles of smooth muscle, which are frequently associated with large caliber blood vessels (Figure 3.16). Muscularis mucosae invasion (pT1) should not be mistaken for muscularis propria invasion (pT2), and it is unacceptable to simply state smooth muscle invasion in the pathology report, at the present time. The presence or absence of muscularis propria should also be mentioned in the pathology report for the adequacy of resection.[14]

The nature of submitted specimens is important in assessing pT1 tumors. Most bladder tumors are frequently excised by cold cup biopsies and TURBT. The resulting hematoxylin and eosin (H&E) sections in cold cup biopsies usually contain urothelial neoplasm (usually <1 cm in diameter), the lamina propria, and sometimes the
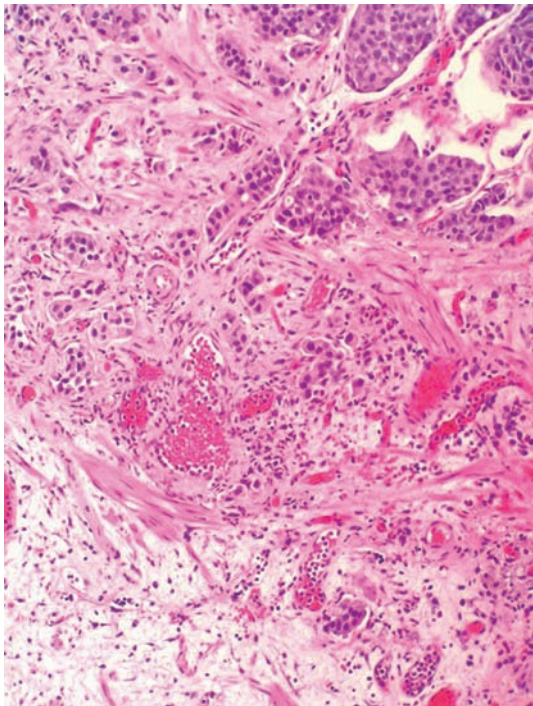
Figure 3.16
Invasive urothelial carcinoma, stage pT1, with tumor cells in contact with the muscularis mucosae.

superficial muscularis propria with maintained orientation, thus facilitating assessment of early invasion. Larger tumors (>1 cm) usually require TURBT, in which the urologist should include a generous sampling of the underlying muscularis propria in order to enable adequate pathologic staging. The specimens resulting from this procedure are often fragmented, heavily cauterized, and tangentially sectioned with frequent disruption of the tumor architecture, and thus may be difficult to orient. While examining and reporting both types of specimens, it is important to note the presence or absence of muscularis propria in the pathology report, in order to assess involvement by the neoplastic process, and to provide feedback to the urologist regarding adequacy of resection.

An additional feature of importance in the evaluation of bladder tumor specimens is the presence of vascular invasion, which can involve blood vessels or lymphatic channels.[14] The identification of vascular/lymphatic invasion can be difficult and confused with artefactual clefting around nests of invasive carcinoma on conventional evaluation. Because vascular invasion is frequently overdiagnosed in H&E stained slides, the reported prognostic significance of that factor remains uncertain. In suspicious cases, blood vessels should be highlighted with immunoperoxidase staining for factor VIII related antigen or, more appropriately, by using monoclonal antibodies against CD31 or CD34.[14] Staining will not resolve the problem of differentiating lymphatic versus artifactual space entrapment by tumor cells in selected cases, and this type of involvement should be reported as indeterminate for vascular invasion.

The incidence of vascular/lymphatic invasion is variable and has been reported to range from 5 to 10% of stage pT1 cases in immunohistochemical studies. In one study, 5-year survival for pT1 cases without vascular invasion was 81% versus 44% for those with, suggesting that vascular invasion is an independent predictor of poor outcome regardless of tumor grade. Vascular invasion is more frequent in larger, high-grade tumors without papillary configuration.

The clinical significance of vascular invasion in advanced infiltrating disease is controversial, with some authors reporting differences in biological behavior, even as independent predictors in patients treated with radical cystectomy together with nodal status and tumor stage. Also, lymphatic and vascular invasion might be an independent prognostic factor in organ-confined invasive bladder cancer.[14] Therefore, the presence of vascular/lymphatic invasion should be included in the pathology report. It is of paramount importance to distinguish T1 from Ta tumors. We will discuss briefly the main morphologic diagnostic criteria for invasion into the lamina propria in the following section.

Features in the diagnosis of lamina propria invasion

The recognition of lamina propria invasion by urothelial carcinoma is one of the most challenging fields in surgical pathology, and the pathologist should follow strict criteria in its assessment.[14,55] While evaluating tumor invasion, it is important to focus on the following features. Lamina propria invasion should be carefully evaluated in all high-grade papillary carcinomas. While invasion is not necessarily an unexpected finding in low-grade tumors, it is much more commonly encountered in high-grade lesions, reaching 70–96% in some series. Tangentially sectioned, densely packed, non-invasive papillary tumors exhibit a stroma–epithelial interface that is smooth and regular. In instances of true invasion, one is likely to see variable sized and irregularly shaped nests or individual tumor cells percolating through the stroma. When the specimen includes tangential sections through non-invasive tumor or when urothelial carcinoma involves von Brunn's nests, the basement membrane preserves a regular contour, whereas it is frequently absent or disrupted in cases of true invasion. This feature may be assessed on H&E stains, although, in many cases, additional clues are needed, including the detection of a parallel array of thin-walled vessels that evenly line the basement membrane of non-invasive nests, these being absent in patients with invasive tumors.[55]

The invasive front of the neoplasm may show one of several features: single cells or irregularly shaped nests of tumor within the stroma, and sometimes tentacular or finger-like extensions can be seen arising from the base of the papillary tumor. Frequently, the invading nests appear morphologically different from cells at the base of the non-invasive component of the tumor, with more abundant cytoplasm and often with a higher degree of nuclear pleomorphism. In some cases, particularly in microinvasive disease, the invasive tumor cells may acquire abundant eosinophilic cytoplasm. At low to medium power magnification, these microinvasive cells seem to be more differentiated than the overlying non-invasive disease, a feature known as paradoxical differentiation. The stromal reaction in the lamina propria associated with invasive tumor may be inflammatory, myxoid, or fibrous, and assessment of this provides an important diagnostic clue. Although the majority of bladder tumors with unquestionable lamina propria invasion exhibit some sort of stromal reaction, microinvasive disease usually does not, making its identification even more difficult.[48] In some cases, a retraction artifact around superficially invasive individual tumor cells may mimic angiolymphatic invasion. Often, this finding is focal, and may itself be one of the early signs of invasion into the lamina propria. Lamina propria invasion may elicit a brisk inflammatory response. Numerous inflammatory cells in the lamina propria may obscure the interface between epithelium and stroma. This makes small nests or single cell invasion difficult to recognize. In other

cases, a cellular stroma with spindled fibroblasts, variable collagenization, inflammation, and/or a hypocellular stroma with myxoid background may be seen in invasive urothelial carcinomas. Rarely, the tumor induces an exuberant proliferation of fibroblasts, which may display alarming cellular atypia (similar to giant cell cystitis). This feature, although a helpful clue to invasion, should not be mistaken for the spindle cell component of a sarcomatoid urothelial carcinoma.[14,55]

Morphologic characteristics of invasive (stage T2–4) urothelial carcinoma

Invasive urothelial carcinoma may present as polypoid, sessile, ulcerated, or infiltrative tumor in which the neoplastic cells invade the bladder wall as nests, cords, trabeculae, small clusters, or single cells that are often separated by a desmoplastic stroma.[4] The tumor sometimes grows in a more diffuse, sheet-like pattern, but even in these cases, focal nests and clusters are generally present. The cells show moderate to abundant amphophilic or eosinophilic cytoplasm and large hyperchromatic nuclei. In larger nests, palisading of nuclei may be seen at the edges of the nests. The nucleus is typically pleomorphic and often has irregular contours with angular profiles. Nuclear grooves may be identified in some cells. Nucleoli are highly variable in number and appearance, with some cells containing single or multiple small nucleoli and others having large eosinophilic nucleoli. Foci of marked pleomorphism may be seen, with bizarre and multinuclear tumor cells. Mitotic figures are common, with numerous abnormal forms.[55,85] Invasive tumors are invariably high-grade, although there is a spectrum of some cases exhibiting marked anaplasia with focal giant cell formation. A subset of invasive urothelial carcinomas may exhibit vascular invasion. The most important morphology-based prognostic factors in patients with advanced bladder cancer are tumor stage and lymph node status.[100–105] In an attempt to identify new parameters for assessing prognosis in bladder cancer patients more accurately, Jimenez et al[55] introduced a new morphologic classification of invasive bladder tumors distinguishing three patterns of growth (nodular, trabecular, and infiltrative). Tumors with an infiltrative growth pattern are associated with a worse prognosis than tumors displaying a non-infiltrative (nodular or trabecular) growth pattern. Urothelial carcinoma has a propensity for divergent differentiation with the most common being squamous, followed by glandular. Virtually the whole spectrum of bladder cancer variants may be seen in variable proportions accompanying otherwise typical urothelial carcinoma.[79] The clinical outcome of some of these variants differs from typical urothelial carcinoma; therefore, recognition of these variants is important. Pathologic features of the most common variants of urothelial carcinoma follow.

Histologic variants of invasive urothelial carcinoma

Urothelial carcinoma with mixed differentiation

About 20% of urothelial carcinomas contain areas of glandular or squamous differentiation. Squamous differentiation, defined by the presence of intercellular bridges or keratinization, occurs in 21% of urothelial carcinomas of the bladder (Figure 3.17). Its frequency increases with grade and stage.[79,106–108] Detailed histologic maps of urothelial carcinoma with squamous differentiation have shown that the proportion of the squamous component may vary considerably, with some cases having urothelial carcinoma in situ as the only urothelial component.[108] These cases may have a less favorable response to therapy than pure urothelial carcinoma. Of 91 patients with metastatic carcinoma, 83% with mixed adenocarcinoma and 46% with mixed squamous cell carcinoma experienced disease progression despite intense chemotherapy, whereas it progressed in <30% of patients with pure urothelial carcinoma.[79,106–108] Low-grade urothelial carcinoma with focal squamous differentiation has a higher recurrence rate.[73] Tumors with any identifiable urothelial element are classified as urothelial carcinoma with squamous differentiation, and an estimate of the percentage of the squamous component should be provided. Cytokeratin 14, L1 antigen, and caveolin-1 have been reported as immunohistochemical markers of squamous differentiation.[79]

Glandular differentiation is less common than squamous differentiation and may be present in about 6% of urothelial carcinomas of the bladder.[79,106–108] Glandular differentiation is defined as the presence of true glandular spaces within the tumor (Figure 3.18).
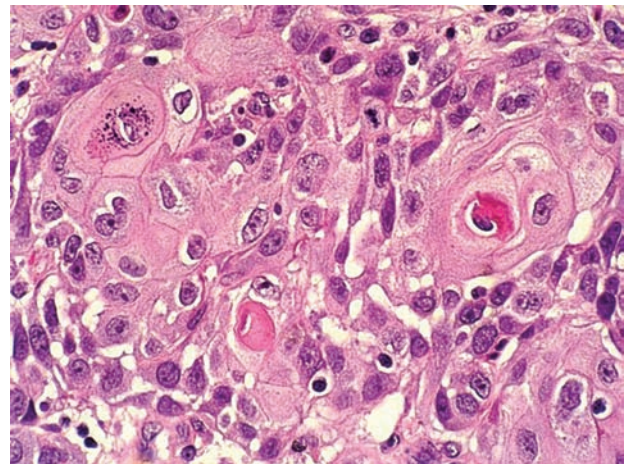

Figure 3.17
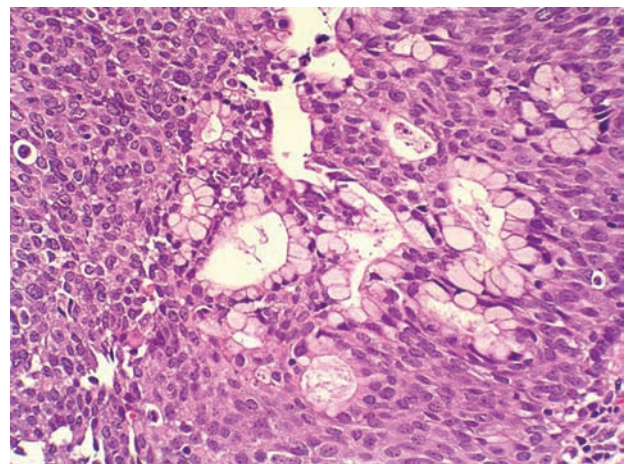Invasive urothelial carcinoma with squamous differentiation.

Figure 3.18
Invasive urothelial carcinoma with glandular differentiation.

These may be tubular or enteric glands with mucin secretion. A colloid-mucinous pattern characterized by nests of cells 'floating' in extracellular mucin, occasionally with signet ring cells, may be present. Cytoplasmic mucin-containing cells are present in 14–63% of typical urothelial carcinoma and are not considered to represent glandular differentiation. The diagnosis of adenocarcinoma is reserved for pure tumors. A tumor with mixed glandular and urothelial differentiation is classified as urothelial carcinoma with glandular differentiation, and an estimate of the percentage of glandular component should be provided. The expression of MUC5AC-apomucin may be useful as an immunohistochemical marker of glandular differentiation in urothelial tumors. When small cell carcinoma is present in association with urothelial carcinoma, even focally, it portends a poor prognosis.[79] Small cell carcinoma is an important finding and usually dictates more aggressive therapy (see following section).

Small cell carcinoma

Small cell carcinoma is a malignant neoplasm derived from the urothelium which mimics its pulmonary counterpart (discussed in full in the section on other bladder carcinomas).

Nested variant

The nested variant of urothelial carcinoma is an aggressive neoplasm with fewer than 50 reported cases[79,109,110] (Figure 3.19). There i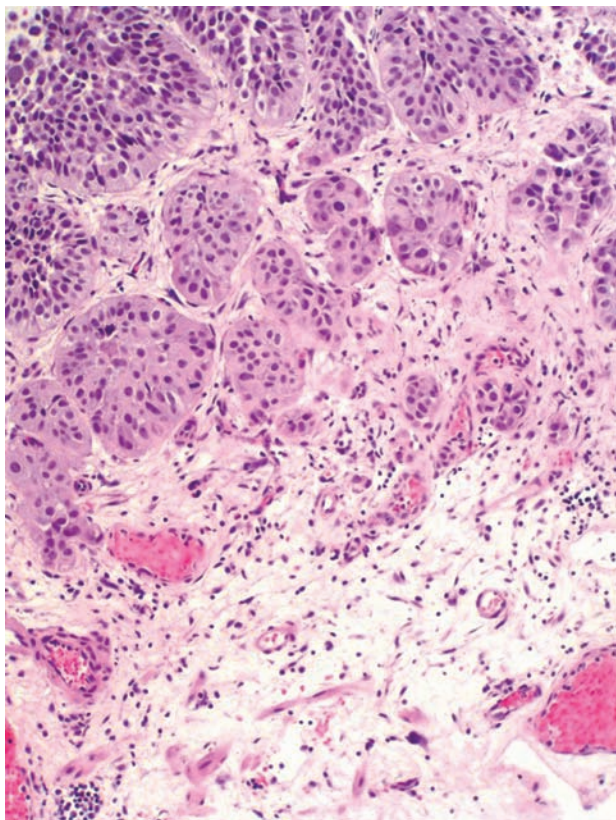s a marked male predominance, and 70% of patients die within 4–40 months after diagnosis, in spite of therapy. This rare pattern of urothelial carcinoma was first described as a tumor with a 'deceptively benign' appearance that closely resembles Brunn's nests infiltrating the lamina propria. Some nests have small tubular lumens that can eventually predominate. Nuclei generally show little or no atypia, but invariably the tumor contains foci of unequivocal cancer with cells exhibiting enlarged nucleoli and coarse nuclear chromatin. This feature is most apparent in the deeper aspects of the cancer. The differential diagnosis of the nested variant of urothelial carcinoma includes prominent Brunn's nests, cystitis cystica and glandularis, inverted papilloma, nephrogenic metaplasia, carcinoid tumor, paraganglionic tissue, and paraganglioma.[79,109,110]

Micropapillary carcinoma

Micropapillary carcinoma is a distinct variant of urothelial carcinoma that resembles papillary serous carcinoma of the ovary, and approximately 60 cases have been reported in the literature (Figure 3.20). There is a male predominance and the ages of the patients range from the fifth to the ninth decade, with a mean age of 66 years.[79,111–113] The most common presenting symptom is hematuria. The first description of micropapillary carcinoma consisted of 18 patients whose ages ranged from 47 to 81 years (mean 67), with a male:female ratio of 5:1. Seven patients died of carcinoma. The micropapillary component is found in association with non-invasive papillary or invasive urothelial carcinoma in 80% of reported cases, consisting of slender delicate filiform processes or small papillary clusters of tumor cells; when present in invasive carcinoma, it is composed of infiltrating tight clusters of micropapillary aggregates that are often within lacunae that are negative for endothelial markers.[79,111–113] Twenty-five percent of cases show glandular differentiation, and some authors consider it as a variant of adenocarcinoma. Psammoma bodies are infrequent. Vascular and lymphatic invasion is common, and most cases show invasion of the muscularis propria or deeper, often with metastases. Immunohistochemical studies in one large series disclosed immunoreactivity of the micropapillary carcinoma in 20 out of 20 cases for epithelial membrane antigen (EMA), cytokeratin 7 and 20, and Leu M-1.[79,111–115] The presence of a surface micropapillary component in bladder biopsy specimens with cancer is an unfavorable prognostic feature, and deeper biopsies may be useful to determine the level of muscle invasion. The main differential consideration is serous micropapillary ovarian carcinoma in women or mesothelioma in both genders.
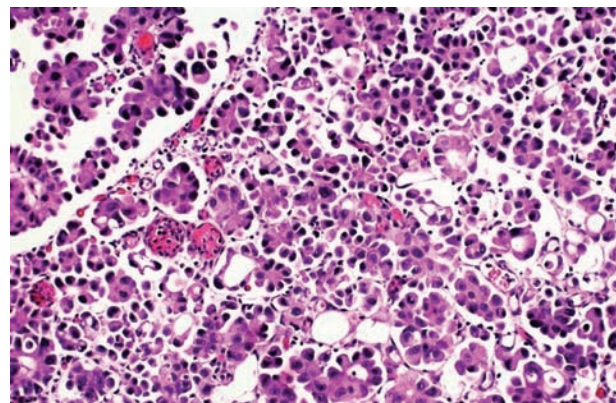

Figure 3.19
Invasive urothelial carcinoma, nested variant.

Figure 3.20
Invasive urothelial carcinoma, micropapillary variant.

Microcystic carcinoma

The microcystic variant of invasive urothelial carcinoma is characterized by the formation of microcysts, macrocysts, or tubular structures with cysts ranging from microscopic up to 1–2 cm in diameter (Figure 3.21). The cysts and tubules may be empty or contain necrotic debris or mucin that stains with periodic acid–Schiff stain with diastase predigestion.[79,111–115] This variant of cancer may be confused with benign proliferations such as florid polypoid cystitis cystica and glandularis and nephrogenic metaplasia. This pattern should be separated from the nested variant of urothelial carcinoma with tubular differentiation.

Lymphoepithelioma-like carcinoma

Carcinoma that histologically resembles lymphoepithelioma of the nasopharynx has recently been described in the urinary bladder, with fewer than 40 cases reported. Disease in the urinary bladder is more common in men than in women (3:1 ratio) and occurs in late adulthood (range 52–81 years, mean 69 years).[79] Most patients present with hematuria. The tumor is solitary and usually involves the dome, posterior wall, or trigone, often with a sessile growth pattern. Histologically, it may be pure or mixed with typical urothelial carcinoma, the latter being focal and inconspicuous in some instances[79,116,117] (Figure 3.22). Glandular and squamous differentiation may be seen.
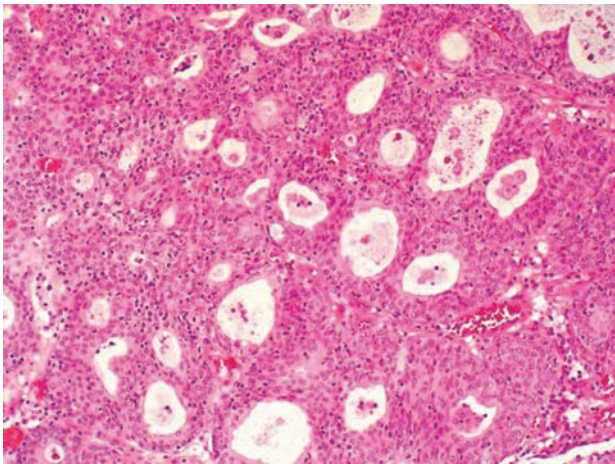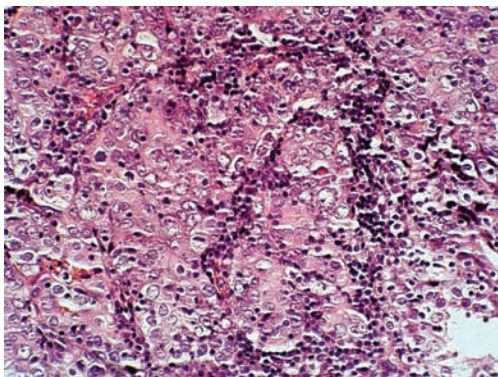
The tumor is composed of nests, sheets, and cords of undifferentiated cells with large pleomorphic nuclei and prominent nucleoli. The cytoplasmic borders are poorly defined, imparting a syncytial appearance. The background consists of a prominent lymphoid stroma that includes T and B lymphocytes, plasma cells, histiocytes, and occasional neutrophils or eosinophils. Epstein–Barr virus infection has not been identified in lymphoepithelioma-like carcinoma of the bladder. This tumor, thus far, has been found to be responsive to chemotherapy when it is encountered in its pure form. The epithelial cells of this tumor stain with several cytokeratin markers as follows: AE1/AE3, CK8, and CK 7, and they are rarely positive for CK20. The major differential diagnostic considerations are poorly differentiated urothelial carcinoma with lymphoid stroma, poorly differentiated squamous cell carcinoma, and lymphoma.

Immunohistochemistry reveals cytokeratin immunoreactivity in the malignant cells, confirming their epithelial nature.[79,116,117] Most reported cases of the urinary bladder have had a relatively favorable prognosis when pure or predominant, but when lymphoepithelioma-like carcinoma is focally present in an otherwise typical urothelial carcinoma, the disease behaves as it does in patients with conventional urothelial carcinoma of the same grade and stage.[117]

Lymphoma-like or plasmacytoma-like carcinoma

Zukerberg et al described bladder carcinoma in two patients that diffusely permeated the bladder wall and was composed of cells with a monotonous appearance mimicking lymphoma. The tumor cells were medium-sized, with eosinophilic cytoplasm and eccentric nuclei producing a plasmacytoid appearance (Figure 3.23). The epithelial nature of the malignancy was confirmed by immunohistochemistry. Differential diagnostic considerations include lymphoma (plasmacytoid type) and multiple myeloma. Identification of an epithelial component confirms the diagnosis. In a series report of six cases, the male:female ratio was 2:1 and the age range was 54–73 years. All cases stained positively for cytokeratin cocktail and cytokeratin 20 and 7, and all were negative for leukocyte common antigen. Five of six patients died of disease (mean survival, 23 months).[79,111–115,118,119]
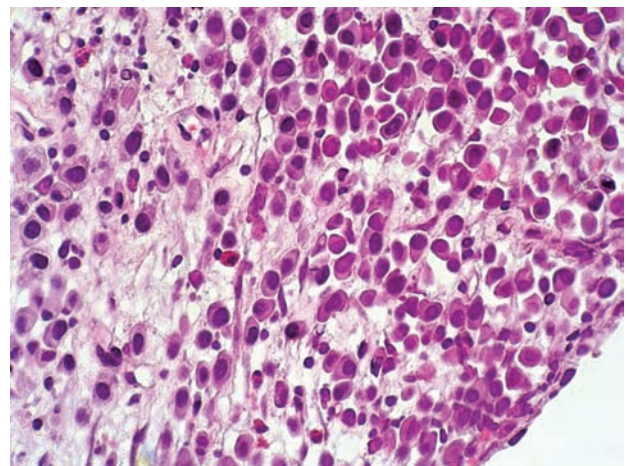

Figure 3.21
Microcystic variant of urothelial carcinoma.

Figure 3.22
Lymphoepithelioma-like carcinoma of the bladder.

Figure 3.23
Plasmacytoma-like carcinoma.

Urothelial carcinoma with endophytic (inverted papilloma-like) growth

The potential for misinterpretation of urothelial carcinoma with endophytic growth as inverted papilloma is high[79,81] (Figure 3.24). By definition, this variant of urothelial carcinoma has significant nuclear pleomorphism, mitotic figures, and architectural abnormalities consistent with low- or high-grade urothelial carcinoma. In most cases, the overlying epithelium has similar abnormalities and often contains typical urothelial carcinoma. Inverted papilloma-type carcinomas with minimal cytologic and architectural abnormalities have high mitotic activity. An exophytic papillary or invasive component is often associated with the inverted element. However, in cases of inverted papilloma fragmented during transurethral resection, a pseudoexophytic pattern may result. In some instances, both inverted papilloma and inverted papilloma-type carcinomas are intimately mixed. Large papillary tumors with prominent endophytic growth 'invade' the lamina propria with a pushing border.[79,81] Unless this pattern is accompanied by true destructive stromal invasion the likelihood of metastasis is minimal, because the basement membrane is not truly breached.

Urothelial carcinoma with syncytiotrophoblastic giant cells

Syncytiotrophoblastic giant cells are present in up to 12% of cases of urothelial carcinoma (Figure 3.25), producing substantial amounts of immunoreactive beta-human chorionic gonadotropin (HCG) indicative of syncytiotrophoblastic differentiation (Figure 3.26). The number of HCG-immunoreactive cells is inversely associated with cancer grade. Secretion of HCG into the serum may be associated with a poor response to radiation therapy. The most important differential diagnostic consideration is choriocarcinoma; most but not all cases previously reported as primary choriocarcinoma of the bladder represent urothelial carcinoma with syncytiotrophoblasts.[79,120,121]
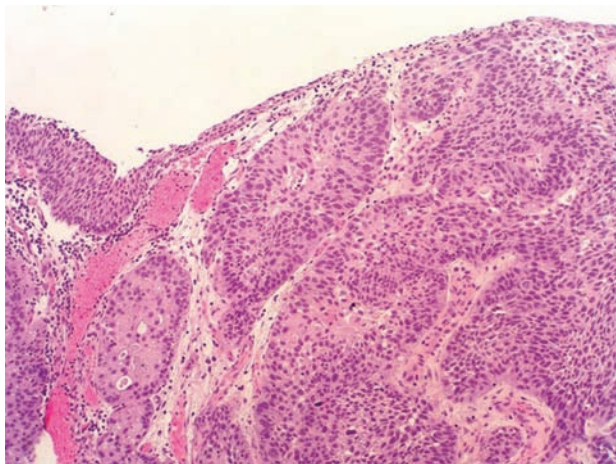

Figure 3.24
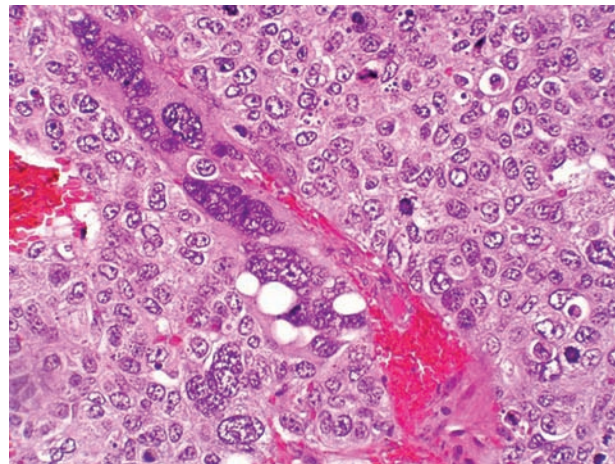Urothelial carcinoma with endophytic (inverted) growth.

Figure 3.25
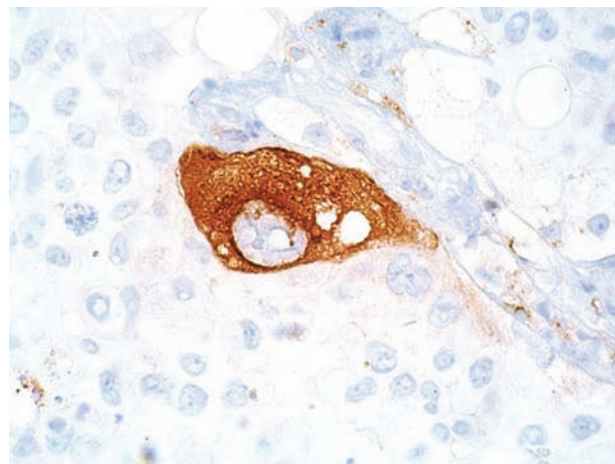Urothelial carcinoma with syncytiotrophoblastic giant cells.

Figure 3.26
Syncytiotrophoblastic giant cells with beta-human chorionic gonadotropin as seen by immunohistochemistry.

Giant cell carcinoma

High-grade urothelial carcinoma may contain epithelial tumor giant cells or the tumor may appear undifferentiated, resembling giant cell carcinoma of the lung (Figure 3.27). This variant is very infrequent. Malignant giant cells in urothelial carcinoma, when present in great numbers, portend a poor prognosis, similar to that associated with giant cell carcinoma in the lung. The giant cells display cytokeratin and vimentin immunoreactivity. The differential diagnosis includes giant cells associated with trophoblastic differentiation, osteoclast-type giant cells in invasive high-grade urothelial carcinoma, sarcomatoid carcinoma with giant cells, and metastatic giant cell carcinoma to the bladder.[79]

Clear cell (glycogen-rich) carcinoma

Up to two-thirds of cases of urothelial carcinoma have foci of clear cell change resulting from abundant glycogen. The glycogen-rich clear cell 'variant' of urothelial carcinoma, recently described, appears to

represent the extreme end of the morphologic spectrum, consisting predominantly or exclusively of cells with abundant clear cytoplasm that stains for cytokeratin 7 (Figure 3.28). Recognition of this pattern avoids confusion with clear cell adenocarcinoma of the bladder and metastatic clear cell carcinoma of the kidney and prostate. Cytoplasmic clearing as a result of thermal artifact should not be mistaken for this variant of bladder cancer.[79,122]
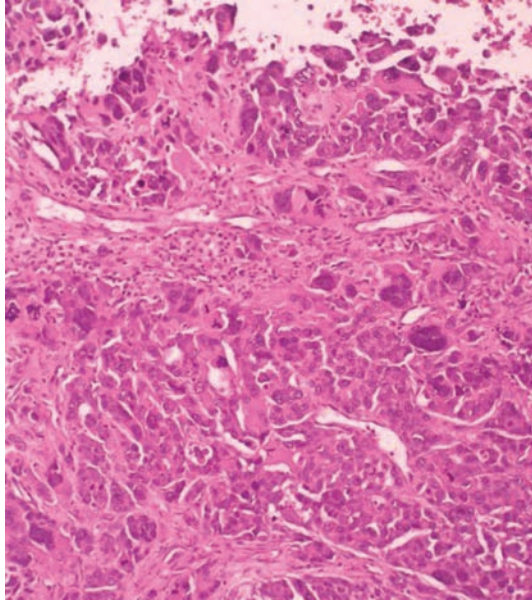

Figure 3.27
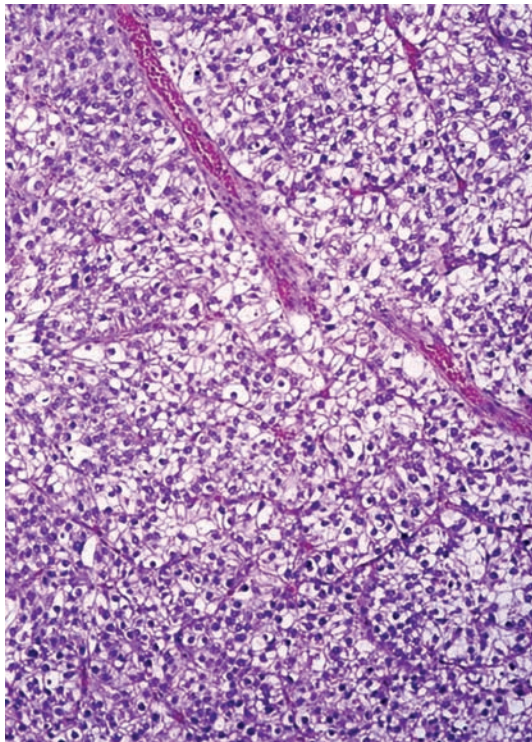Giant cell carcinoma of the bladder.

Figure 3.28
Clear-cell (glycogen-rich) urothelial carcinoma.

Sarcomatoid carcinoma with/without heterologous elements (carcinosarcoma)

The term sarcomatoid variant of urothelial carcinoma should be used for all biphasic malignant neoplasms exhibiting morphologic and/or immunohistochemical evidence of epithelial and mesenchymal differentiation (with the presence or absence of heterologous elements acknowledged in the report)[4,79,120,123–127] (Figure 3.29). There is considerable confusion and disagreement in the literature regarding nomenclature and histogenesis of these tumors. As with other organs, various terms have been used for these neoplasms, including carcinosarcoma, sarcomatoid carcinoma, pseudosarcomatous transitional cell carcinoma, malignant mesodermal mixed tumor, spindle cell carcinoma, giant cell carcinoma, and malignant teratoma. In some series, both carcinosarcoma and sarcomatoid carcinoma are included as 'sarcomatoid carcinoma'. In others they are regarded as separate entities. A previous history of carcinoma treated by radiation or exposure to cyclophosphamide therapy is common.[4,79,120,123–127]

The gross appearance is characteristically 'sarcoma-like', dull gray with infiltrative margins. The tumors are often polypoid with large intraluminal masses. Microscopically, sarcomatoid carcinoma is composed of urothelial, glandular, or small cell component showing variable degrees of differentiation. Carcinoma in situ is present in 30% of cases and occasionally is the only apparent epithelial component. A small subset of sarcomatoid carcinoma may have a prominent myxoid stroma. The mesenchymal component most frequently observed is an undifferentiated high grade spindle cell neoplasm. The most common heterologous element is osteosarcoma followed by chondrosarcoma, rhabdomyosarcoma, leiomyosarcoma, liposarcoma, and angiosarcoma, or multiple types of heterologous differentiation may be present (Figure 3.30).

By immunohistochemistry, epithelial elements react with cytokeratins, whereas stromal elements react with vimentin or specific markers corresponding to the mesenchymal differentiation[4,79,120,123–127] (Table 3.5). The sarcomatoid phenotype retains the epithelial nature of the cells by immunohistochemistry or electron microscopy. Recent molecular studies strongly argue for a monoclonal origin of both components in sarcomatoid carcinoma and carcinosarcoma. These two categories have similar clinical characteristics, including patient age, gender presentation, and outcome. The most frequent presenting signs and symptoms are hematuria, dysuria, nocturia, acute urinary retention, and lower abdominal pain. The mean age is
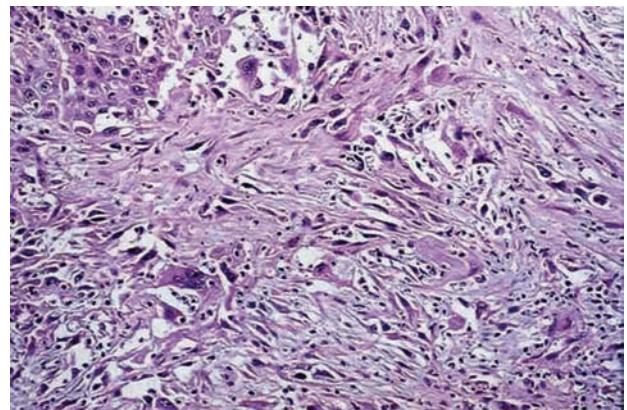

Figure 3.29
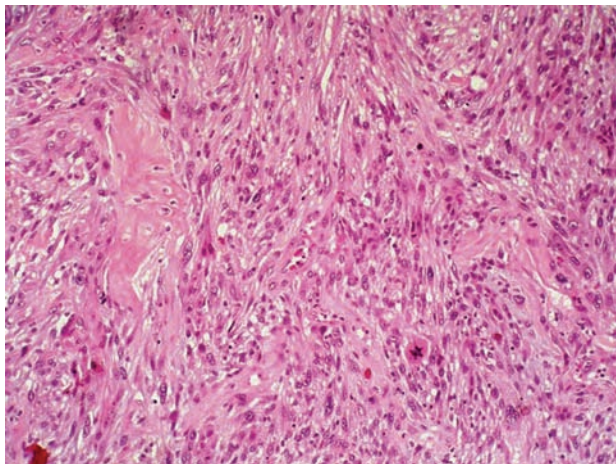Sarcomatoid carcinoma of the bladder.

Figure 3.30
Osteosarcomatous differentiation in a case of sarcomatoid
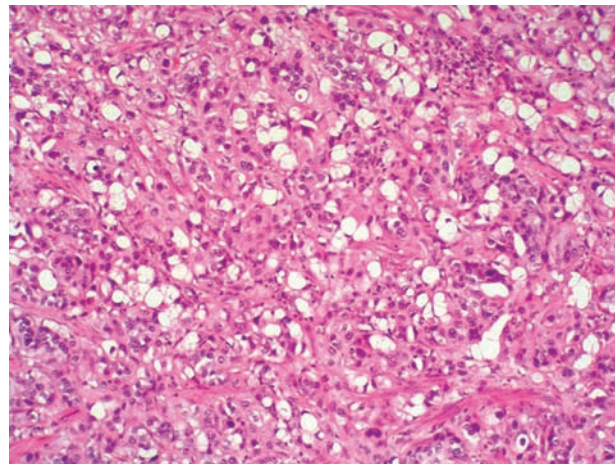carcinoma of the bladder.

Figure 3.31
Invasive urothelial carcinoma, lipoid-cell variant.

Table 3.5 Immunohistochemical profiles of spindle cell lesions of the bladder

	CK	SMA/MSA/ desmin	EMA	Vimentin	ALK-1
Postoperative spindle cell nodule	−/+	+/−	−	+	−
Inflammatory myofibroblastic tumor	−/+	+/−	−	+	+
Malakoplakia and caruncle	−	−	−	+	−
Sarcomatoid carcinoma	+	+	+	+	−
Leiomyosarcoma	−	+	−	+	−
Lymphoepithelioma-like carcinoma	+	−	+	+	−

CK = cytokeratin; SMA = smooth muscle actin; MSA = muscle-specific actin; EMA = epithelial membrane antigen; ALK1 = anaplastic lymphoma kinase 1.

66 years (range 50–77 years). Pathologic stage is the best predictor of survival in sarcomatoid carcinoma. The major differential diagnostic consideration is urothelial carcinoma with pseudosarcomatous stroma, a rare entity with reactive stroma. In cases with exclusively spindle cells, the main differential diagnostic consideration is sarcoma, particularly leiomyosarcoma. The rarity of primary bladder sarcoma warrants that any malignant spindle cell tumor in the urinary bladder in an adult be considered sarcomatoid carcinoma until proven otherwise. Immunostaining with cytokeratin is helpful in this setting. Sarcomatoid carcinoma with prominent myxoid and sclerosing stroma may be mistaken for inflammatory pseudotumor.[4,79,120,123–127]

Lipoid cell variant

Lipoid cell variant is a rare neoplasm defined by the WHO (1999, 2004)[4,59,79] as a urothelial carcinoma which exhibits transition to a cell type resembling signet-ring lipoblasts (Figure 3.31). It is currently considered to be an ill-defined tumor variant, and whether it should be classified as carcinosarcoma remains to be established. Clinico-pathologic features and the immunohistochemical findings in seven reported cases showed gross hematuria as the initial symptom. All patients were elderly men (mean age 74 years; range 63–94 years). On microscopic examination, the extension of the lipid cell pattern varied from 10 to 30% of the tumor specimen, with associated micropapillary ($n = 1$), plasmocytoid ($n = 2$), and grade 3/3 conventional urothelial carcinomas ($n = 4$). The immunohistochemical results showed an epithelial phenotype of the lipoid cell component characterized by diffuse staining with cytokeratins AE1/AE3. The reported cases were pathologic stage T2 ($n = 2$), T3a ($n = 1$), T3b ($n = 3$), and T4 ($n = 1$). Patient follow-up showed one dead and two alive with disease at 58, 14, and 55 months, respectively.[4,79] Two patients showed no evidence of disease at 11 and 29 months. Two additional patients died of other causes at 10 and 15 months.

Undifferentiated carcinoma

This category contains tumors that cannot be otherwise classified. To our knowledge, they are extremely rare.[79] Earlier literature has reported small cell carcinoma, giant cell carcinoma, and lymphoepithelioma-like carcinoma in this category, but these tumors are now recognized as specific tumor variants (see respective sections). Large cell undifferentiated carcinomas as in the lung are rare in the urinary tract, and those with neuroendocrine features should be recognized as a specific tumor variant. Rare cases showing multinucleated giant cells or a streaking rhabdoid phenotype have been recently recognized.[79,128,129]

Urothelial carcinoma with prominent stromal reaction

Infiltrating urothelial carcinoma may be associated with a variety of stromal reactions, which are occasionally pronounced. Urothelial

carcinoma may have a pseudosarcomatous stroma, which rarely displays sufficient cellularity, cytologic atypia, spindle cell proliferation, or myxoid appearance to raise serious concern about sarcomatoid carcinoma. The stromal cells reveal immunohistochemical evidence of fibroblastic or myofibroblastic differentiation and invariably are cytokeratin negative or focally positive.[4,79,118,120,123–127] Tumor-associated osseous and/or chondroid metaplasia is present in some cases of urothelial carcinoma and its metastases, and this should be differentiated from osteosarcoma or chondrosarcoma. The metaplastic bone or cartilage is histologically benign. Zukerberg et al[118] described the presence of osteoclast-like giant cells in two cases of invasive high-grade urothelial carcinoma; a finding rarely reported.[76,128] The giant cells had abundant eosinophilic cytoplasm and numerous small, round, regular nuclei and displayed immunoreactivity for vimentin and CD68 but not for epithelial markers. It seems not to be related to prognosis. An inflammatory cell response in the stroma adjacent to the invasive tumors is relatively common. This response usually takes the form of a lymphocytic infiltrate with a variable admixture of plasma cells. Generally, this cellular reaction is mild to moderate, but occasionally it may be dense. Sometimes a neutrophilic response is observed, with or without extensive eosinophilic infiltrate, suggesting that, in the absence of a cellular response, the carcinoma is likely to be more aggressive. In a recent study, intense inflammation in bladder carcinoma was found to be associated with tumor angiogenesis and indicative of a good prognosis. Exclusion of lymphoepithelioma-like carcinoma of the urinary bladder is mandatory when there is extensive inflammation in the stroma.[79,130–134]

Prognostic morphologic factors

Grade

Several studies have investigated the role of tumor grade on tumor recurrence, progression, and mortality. The majority have demonstrated that grade is a better prognostic indicator of progression and mortality than recurrence,[4,20,85,135] in particular grade 3 disease, which is in some studies the main predictor of progression and mortality. Simlarly, progression rates of 2%, 11%, and 45% for grade 1, 2, and 3 diseases, respectively, have been reported.[15,53,54,64,85,136,137] Furthermore, when stratified by stage of disease, tumor grade has been correlated with mortality. Jakse et al reported the following 10-year survival rates for patients with initial stage Ta or T1 disease: 95% for TaG1 compared to 84% for TaG3; and 78% for T1G2 compared to 50% T1G3[2–4] (Table 3.6).

Stage

Since Ta tumors are, by definition, confined to the basement membrane without access to lymphatics and vessels, these lesions tend to remain localized[2] (Table 3.7). The National Bladder Cancer Cooperative Group studies of the 1970s provide some insight into the natural course of superficial bladder cancer with regard to stage following TUR and no adjuvant intravesical therapy. Recurrence with progression to muscle invasion was found within 3 years in only 4% of patients with initial Ta tumors (without associated atypia or CIS) and 11% of Ta tumors with associated atypia.[4,25,34,85,99,103]

Table 3.6 Current prognostic factors in bladder cancer

Number of tumors
Cancer size >5 cm in diameter
Tumor extent (stage)
Histologic grade
Coexistent dysplasia or CIS
Tumor growth pattern
Vascular/lymphatic invasion
Lymph node involvement
Recurrence at 3-month follow-up cystoscopy
Molecular markers (p53, RB, cadherins, p63, cyclin D1, cyclin D3 and others)
Others: DNA ploidy, Ki67-MIB1

Table 3.7 TNM classification of bladder cancer (2002 revision)[83]

Primary tumor (T): urinary bladder

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Papillary non-invasive carcinoma
Tis	Carcinoma in situ: 'flat tumor'
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades muscle
T2a	Tumor invades superficial muscle (inner half)
T2b	Tumor invades deep muscle (outer half)
T3	Tumor invades perivesical tissue
T3a	Microscopically
T3b	Macroscopically (extravesical mass)
T4	Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, and abdominal wall
T4a	Tumor invades prostate or uterus or vagina
T4b	Tumor invades pelvic wall or abdominal wall

The suffix 'm' should be added to the appropriate T category to indicate multiple tumors. The suffix 'is' may be added to any T to indicate the presence of associated carcinoma in situ

Regional lymph nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases in a single lymph node, 2 cm or less in greatest dimension
N2	Metastases in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, none more than 5 cm in greatest dimension
N3	Metastasis in a lymph node more than 5 cm in greatest dimension

Distant metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Patients with low-grade Ta disease have a propensity for tumor recurrence despite low progression rates. In a long-term follow-up study of 255 patients with low-grade Ta disease, approximately 70% of patients had repeat resections for tumor recurrence whereas only 2% of patients progressed to muscle invasive disease.[24,53,54] When these patients were subclassified based on the new WHO/ISUP classification system 37% were PUNLMP and 63% were low-grade urothelial carcinomas. As expected, recurrence rates of PUNLMP were significantly lower that those with low-grade urothelial carcinoma, 35% vs 71%, respectively.[24,53,54] The incidence of high-grade Ta lesions is rare, and varies between 2 and 9% of all cases of superficial bladder cancer. Despite the relatively low malignant potential component of being Ta, it is the high-grade component that has a significant impact on progression and poses a considerable problem for the clinician. Even with intravesical treatments, nearly 50% recur, 25% progress to muscle invasive disease, and 4% can cause mortality. Therefore, these lesions should be regarded as malignant, and demand vigorous treatment and follow-up.[24,53,54]

Most T1 bladder cancers are high-grade lesions with potential for recurrence, progression, and death.[24,53,54] These lesions are frequently understaged or misclassified. van Der Meijden et al[95] assessed pathology results from 1400 patients treated in European Organization for Research and Treatment of Cancer randomized trials comparing various treatment strategies for superficial bladder cancer. In this study, 10% of patients originally staged T1 by local pathologists were found to have evidence of muscle invasion on review.[95] Furthermore, tumors that lack muscle in the initial resected specimen are subsequently associated with residual tumor burden or muscle-invasive disease at repeat resection in up to one half of cases. Importantly, a second TUR for T1 tumors is recommended as at least 30% of patients with T1 disease will be upstaged at the time of second TUR, and even higher if no muscle is present in the original TUR specimen.[95] The risk of residual tumor on second TUR is also significant. Therefore, for patients with T1 disease, a second TUR should be performed within 1 to 4 weeks following the initial resection. A third of patients with T1 tumors eventually progress to muscle-invasive disease. Furthermore, as aforementioned, the depth of submucosal invasion may be prognostically significant. The prognosis of high-grade T1 tumors is variable and multifactorial, based on additional tumor histopathologic characteristics.[95] The presence of concomitant CIS confers a particularly poor prognosis, with up to 80% progressing to muscle-invasive disease. It is clear that high-grade T1 disease represents a potentially lethal disease class that may warrant early radical cystectomy, particularly when conservative management with intravesical therapy fails. Pathologic staging is the most important regarding risk assessment and in dictating patient management.[95]

Carcinoma in situ

The presence of associated CIS may be ominous, as patients are at increased risk of progression and death from bladder cancer.[19] In one study, the recurrence rate increased to 73% in patients with dysplasia or CIS, compared to a 43% recurrence rate without CIS. One half of patients presenting with either diffuse and symptomatic CIS or with associated papillary lesions progress to muscle-invasive disease, and as many as 40% will ultimately die of bladder cancer. Patients who present with marked urinary symptoms generally have a shorter interval preceding the development of muscle-invasive cancer. Reliable prognostic factors that predict the course of CIS do not currently exist; however, some studies have suggested that

response to intravesical chemotherapy or immunotherapy can be used to predict progression and death from the disease.[19]

Number of tumors

The number of tumors is an important risk factor for tumor recurrence. Recurrences for solitary bladder tumors vary from 18 to 60%, while rates for multiple tumors ranges from 40 to 90%. In a multivariate analysis of prognostic variables, Herr reported that the factor most predictive of recurrence is tumor multifocality, while tumor stage and grade correlated to a lesser degree.[101,136]

Size

Tumor size may be a prognostic factor for superficial bladder cancer, with a reported progression to muscle invasion seen in 35% of patients with superficial tumors larger than 5 cm, compared to only 9% of patients with small bladder tumors.[32,51,53,54] Others report that tumor size may influence tumor stage, but not progression.[2–4,136]

Other prognostic factors

Time to first bladder cancer recurrence may also be an important variable. In a group of 414 Ta tumors, it was reported that if no recurrence occurred in the first follow-up cystoscopy, 79% had no further recurrence for the remainder of the follow-up. However, in patients with a follow-up recurrence at 3 months, only 10% were without any recurrence during the remainder of the follow-up period.[2–4] In addition, as reported above, the presence of vascular or lymphatic invasion has been identified as a poor prognostic sign.[85,102,103] Although lymphovascular invasion may be difficult to ascertain due to interobserver variability and the fact that it could be confused with retraction artifact, it has been shown to increase the risk of death to 70% with the presence of vascular invasion. Recent data suggest that removal of more lymph nodes may provide a better outcome, as well as more accurate pathologic findings, in patients with bladder cancer. Also, extracapsular extension of pelvic lymph node metastasis in patients with surgically treated bladder cancer could be an important prognostic factor.[85,102,103]

Based on previously established data, some risk group classification systems or nomograms combining the aforementioned prognostic factors have been suggested. By combining stage and grade, risk groups were classified as low – grade 1 stage Ta disease and a single grade 1 stage T1 tumor; intermediate – multiple grade 1 stage T1 tumors, grade 2 stage Ta disease or a single grade 2 stage T1 tumor; and high – multiple grade 2 stage T1 tumors, grade 3 stages Ta or T1 disease, and any stage disease associated with CIS. Recurrence, progression, and overall survival were significantly different among the three groups. Low-risk and intermediate-risk patients demonstrated 37% and 45% risk of recurrence, respectively, without significant risk for progression or death from bladder cancer. On the other hand, in the high-risk category, risk of recurrence, progression and mortality was 54%, 15%, and 9.5%, respectively. Similarly, a combined analysis of patients from seven EORTC trials facilitated the calculation of short- and long-term risks of recurrence and progression based on multiple factors including stage, grade, presence of CIS, multifocality, size, and history of prior recurrence[21,25] findings that should be reported (Table 3.8).

Table 3.8 Practice parameters for handling and reporting bladder specimens with cancer (checklist)

General information

■ Pertinent clinical information: name, medical record number, data, referring physician, relevant clinical history past and present

Gross description

■ Fresh or fixed specimen
■ Nature of the specimen: biopsy, chips (TURB), partial cystectomy, radical cystectomy, cystoprostatectomy, 'en bloc' resection
■ Total weight of resected tissue fragments (TURB); three-dimensional measurements of recognizable anatomic structures and tumors or other recognizable lesions
■ Site of involvement, gross fat extension

Diagnostic and prognostic information

■ Histologic tumor type: urothelial, squamous, adenocarcinoma, other
■ Tumor grade: use current grading schemes (WHO 2004, WHO 1973, or both)
■ Extent of tumor in bladder (degree of invasion)*
■ No invasion
■ Invasion of the suburothelial connective tissue, muscularis propria, perivesical tissue
■ Presence or absence of lymphatic/vascular invasion
■ Tumor arising in a diverticulum (state whether muscularis propria is present)
　■ intraepithelial abnormalities (dysplasia, CIS)
　■ report focality or multifocality
■ Report presence of pagetoid spread of CIS (this finding is not dysplasia)
　■ extent of tumor in organs attached to the bladder
■ Prostate: direct extension to the prostate, involvement of prostatic urethra, involvement of prostatic ducts with or without stromal involvement
■ Ureter and urethra: report any dysplastic/neoplastic change of the mucosa, and report any invasion into adjacent suburothelial connective tissue or muscularis propria
■ Seminal vesicles: report spread of carcinoma in these organs either through epithelium or by direct extension of an infiltrative tumor
■ Vagina/uterus: report direct extension or metastasis to either organ
■ Surgical margins: report status of ureteral/urethral margins. Report perivesical margin involvement
■ Report important associated conditions such PIN and adenocarcinoma of the prostate
■ Lymph nodes: report presence or absence of metastasis. If metastases are present state number and size of the largest one (<2.0 cm, 2.1–5 cm, >5 cm)

Features considered optional in the final report

■ Invasion of the muscularis mucosa, if present; T1 substaging with micrometer, or just focal/wide suburothelial connective tissue invasion
■ Genetic abnormalities
■ Cytometric examination
■ Morphometric examination

(*Continued*)

Table 3.8 (Continued)

■ p53, ki-67
■ Growth factors and receptors
■ Other immunohistochemical markers
■ Stage: use TNM/AJCC 2002 revision (T1–T4, N, and M)

*Immunohistochemistry may be useful in selected cases using either cytokeratin for suburothelial connective tissue invasion or vascular endothelial markers for vascular invasion.

Other carcinomas of the urinary bladder

Squamous cell carcinoma

A malignant neoplasm derived from the urothelium showing histologically pure squamous cell phenotype[137,138] (Figure 3.32). Schistosomiasis and chronic urinary tract infection are conditions associated with the development of squamous cell carcinoma. If an identifiable urothelial element including urothelial CIS is found, the tumor should be classified as urothelial carcinoma with squamous differentiation. The presence of keratinizing squamous metaplasia in the adjacent flat epithelium, especially if associated with dysplasia, supports a diagnosis of squamous cell carcinoma. The invasive tumors may be well differentiated with well-defined islands of squamous cells with keratinization, prominent intercellular bridges, and minimal nuclear pleomorphism. They may also be poorly differentiated, with marked nuclear pleomorphism and only focal evidence of squamous differentiation. The verrucous form of squamous cell carcinoma is an uncommon variant that occurs most frequently in patients with schistosomiasis, accounting for 3 to 4.6% of bladder cancers in such a setting; however, isolated cases have been described in the literature from non-endemic areas[137,138] (Figure 3.33). Rare cases in the literature have a verrucous-like morphology with some invasive component.[138] It is recommended not to diagnose these cases as verrucous carcinoma. A basaloid pattern of squamous cell carcinoma has been reported, and a clear cell pattern of squamous cell carcinoma of the bladder is under discussion. T-stage, lymph node involvement, and tumor grade have been shown to be of independent prognostic value. Patients undergoing radical surgery appear to have an improved survival as compared to radiation therapy and/or chemotherapy.[137,138]

Primary adenocarcinoma

A malignant neoplasm derived from the urothelium showing histologically pure glandular phenotype[122,139–146] (Figure 3.34). It accounts for 0.5–2% of all malignant bladder tumors and two major categories have been recognized: (1) those arising in the bladder proper and (2) those arising from the urachal remnants.[146] Adenocarcinoma of the urinary bladder occurs more commonly in males than in females, with a peak incidence in the sixth decade of life. Hematuria is common. Adenocarcinoma of the bladder may show different patterns of growth; these include: (1) enteric (colonic) type, (2) adenocarcinoma not otherwise specified (NOS), (3) signet-ring cell, (4) mucinous (colloid), (5) clear cell, (6) hepatoid, and (7) mixed forms. The NOS type consists of an adenocarcinoma with a non-specific
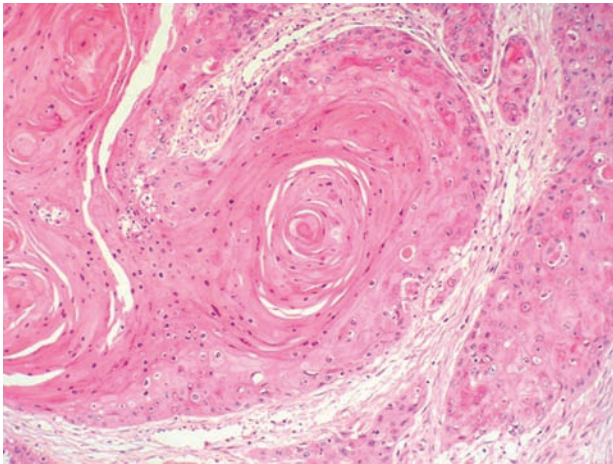
Figure 3.32
Well-differentiated squamous cell carcinoma of the urinary bladder.

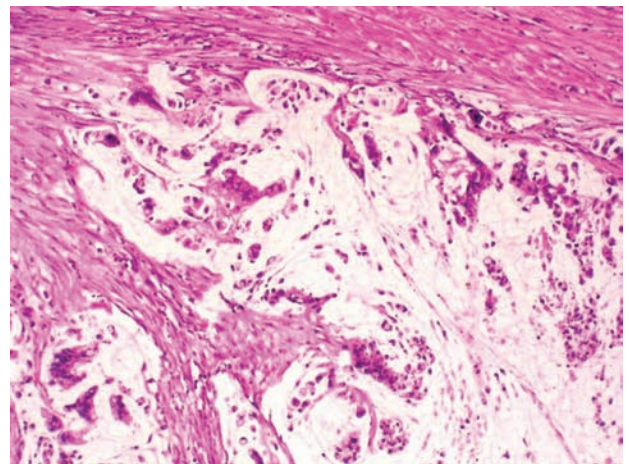**Figure 3.33**
Squamous cell carcinoma of the urinary bladder, verrucous type.

Figure 3.34
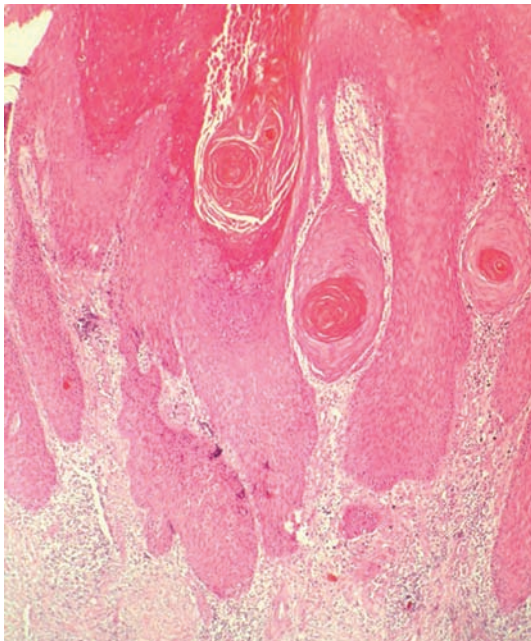Primary mucinous adenocarcinoma of the bladder arising in the urachus.

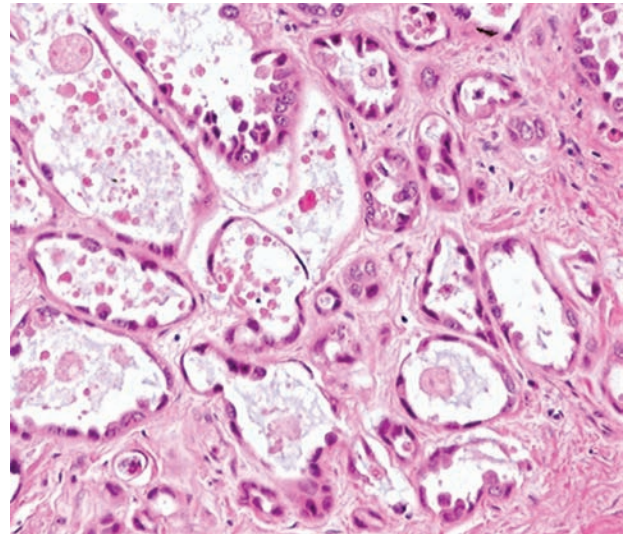**Figure 3.35**
Clear cell adenocarcinoma of the bladder.

Figure 3.36
Hepatoid adenocarcinoma of the bladder.

glandular growth. The enteric type closely resembles adenocarcinoma of the colon.[122,139–146] Tumors that show abundant mucin with tumor cells floating within the mucin are classified as mucinous or colloid type. The signet-ring cell variant may be diffuse or mixed, and can have a monocytoid or plasmacytoid phenotype. An extremely rare variant of adenocarcinoma is the clear cell type (mesonephric), which consists of papillary structures with cells that exhibit a hobnail appearance[122,139–144] (Figure 3.35). The hepatoid type (Figure 3.36) is also rare and consists of large cells with eosinophilic cytoplasm that are reactive for alpha-fetoprotein[141] (Figure 3.37). Finally, it is not uncommon to find a mixture of these growth patterns. Adenocarcinoma in situ may be found in the urinary bladder alone or in combination with an invasive adenocarcinoma.
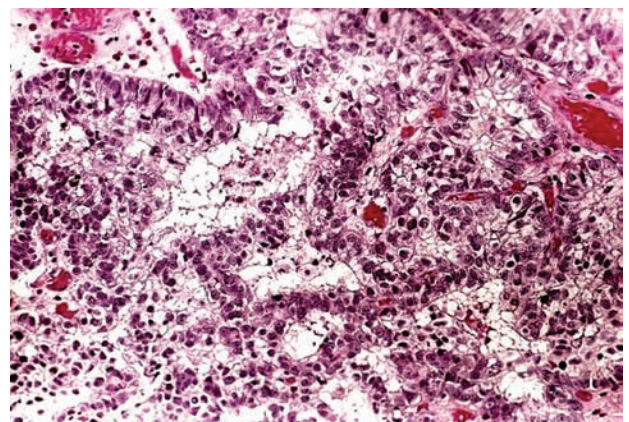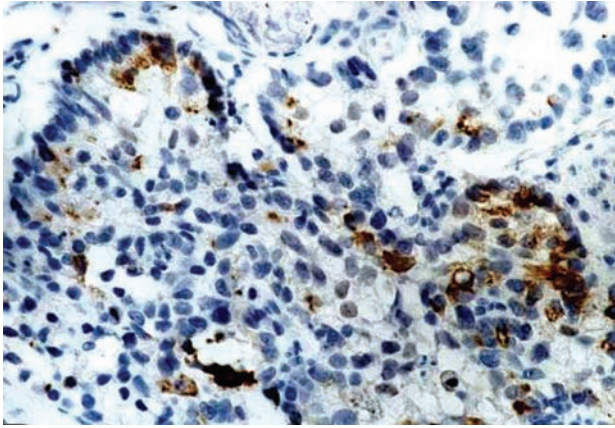
Figure 3.37
Hepatoid adenocarcinoma of the bladder, alpha-fetoprotein immunohistochemistry.

There is no generally accepted grading system ascribed to adenocarcinoma of the bladder. The immunohistochemical profile of these tumors that has been reported in the literature is variable and closely matches that of colonic adenocarcinomas including its neuroendocrine differentiation. Reports of CK 7 positivity are variable, while CK-20 is reported to be positive in most bladder adenocarcinomas. Villin has recently been reported to be positive in enteric type adenocarcinomas of the urinary bladder and beta-catenin has been reported to be of help in distinguishing primary adenocarcinoma of the bladder from metastatic colonic adenocarcinoma.[133] Stage is the most important prognostic factor. It is important to distinguish between urachal and non-urachal adenocarcinomas, especially for treatment purposes. Among histologic types of adenocarcinoma, pure signet-ring cell carcinoma carries the worst prognosis.[145]

Small cell carcinoma

Small cell carcinoma is a malignant neuroendocrine neoplasm derived from the urothelium which histologically mimics its pulmonary counterpart[79] (Figure 3.38). In a recent series of 64 cases of small cell carcinoma of the urinary bladder all the patients except one had muscle-invasive disease at presentation.[5,147] Thirty-eight patients (59%) underwent cystectomy and 66% of patients had lymph
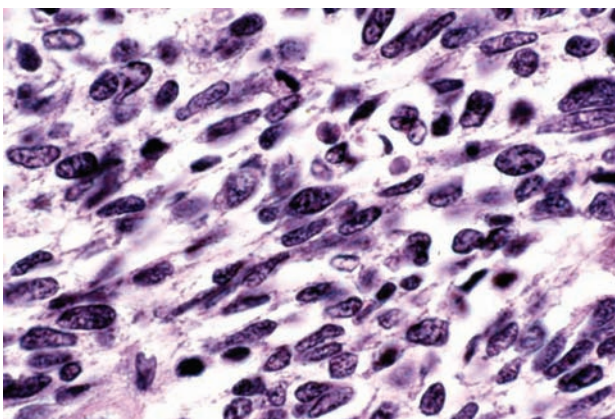

Figure 3.38
Small cell carcinoma of the bladder.

node metastasis at the time of cystectomy with regional lymph nodes, bone, liver, and lung being the most common locations. Twenty cases (32%) were pure small cell carcinoma and 44 cases (68%) consisted of small cell carcinoma with other histologic types (urothelial carcinoma, 35 cases; adenocarcinoma, 4 cases; sarcomatoid urothelial carcinoma, 2 cases; and 3 cases with both adenocarcinoma and urothelial carcinoma). Patients with organ-confined cancers had marginally better survival than those with non-organ-confined cancer ($p = 0.06$).[5] At gross examination, most tumors appear as a large solid, isolated, polypoid, nodular mass with or without ulceration, and may extensively infiltrate the bladder wall. The vesical lateral walls and the dome are the most frequent topographies but rare cases may arise in a diverticulum.

At histology, they consist of small, rather uniform cells, with nuclear molding, scant cytoplasm, and nuclei containing finely stippled chromatin and inconspicuous nucleoli. Mitoses are present and may be frequent. Necrosis is common and there may be DNA encrustation of blood vessels walls (Azzopardi phenomenon). Most cases have areas of urothelial carcinoma, sometimes in the form of flat urothelial carcinoma in situ and, exceptionally, squamous cell carcinoma, adenocarcinoma, or sarcomatoid carcinoma.[147] The immunohistochemical profile reveals neuronal-specific enolase in 87% of cases, and chromogranin A only in a third of cases. Some cases are also reactive against synaptophysin, PGP 9.5, thyroid transcription factor-1 (TTF-1), p53 (DO7), and Ki67 (MIB-1).[148] The finding of c-kit and c-erbB2 expression by immunohistochemistry opens new possibilities for therapy in small cell carcinoma of the bladder.[149]

The prognosis of small cell carcinoma of the urinary bladder remains poor irrespective of therapy. Electrolyte abnormalities such as hypercalcemia or hypophosphatemia, and ectopic secretion of ACTH, have also been reported as part of the paraneoplastic syndrome associated with primary small cell carcinoma of the bladder. The diagnosis of small cell carcinoma can be made on morphologic grounds alone, even if neuroendocrine differentiation cannot be demonstrated. Frequently, small cell carcinoma expresses cytokeratin which supports the hypothesis of urothelial origin.[147] Data obtained by comparative genomic hybridization suggest that urinary bladder small cell carcinoma is a genetically unstable tumor, typically exhibiting a high number of cytogenetic abnormalities. The differential diagnosis is metastasis of a small cell carcinoma from another site, lymphoma, lymphoepithelioma-like carcinoma, plasmacytoid carcinoma, and a poorly differentiated urothelial carcinoma.[5]

Secondary carcinoma involving the bladder

Practicing pathologists should be aware of the incidence and histologic appearances of secondary neoplasms of the urinary bladder, with emphasis on the points of distinction from primary tumors and their histologic variants.[149] In a retrospective study of 282 tumors, secondary bladder neoplasms represented 2.3% of all malignant bladder tumors in surgical specimens at one institution.[149] The commonest primary sites were the colon (21% of secondary neoplasms), prostate (19%), rectum (12%), and cervix (11%). Most tumors from these sites reached the bladder by direct spread. The most common distant sites of origin of tumors metastatic to the bladder were stomach (4.3% of all secondary bladder neoplasms), skin (3.9%), lung (2.8%), and breast (2.5%). Secondary tumor deposits were almost always solitary (96.7%), and 54% were located in the bladder neck or trigone. Histologically, 54% of secondary tumors were adenocarcinomas. Immunohistochemical staining patterns with prostate-specific

acid phosphatase, prostate-specific antigen, carcinoembryonic antigen, chromogranin, and neurone-specific enolase were similar in primary vesical and urachal adenocarcinomas and secondary adenocarcinomas from the gastrointestinal tract. It was concluded that the incidence of secondary bladder tumors is comparable to that of primary non-urothelial carcinomas.[149]

Differential diagnosis

Few secondary tumors have distinctive histologic features making it difficult to make the appropriate diagnosis, hence knowledge of the history and clinical investigation are particularly important in these cases.

Immunohistochemistry is extremely important in distinguishing primary tumors of the urinary bladder from metastasis. A particularly important exercise is the differential diagnosis of glandular tumors that can occur primarily and secondarily in the bladder. In addition to clinical information which is essential, some immunohistochemical markers have been proposed in the recent literature to assist in this differential; i.e. urothelial carcinoma with glandular differentiation can be distinguished from colonic adenocarcinoma because the former is CK7-positive, CK20-positive, and villin-negative, whereas the latter is CK20-positive, villin-positive, and CK7-negative; lack of CDX2 and villin immunostaining signals points strongly to a bladder primary adenocarcinoma.[79,98] Prostate adenocarcinoma rarely represents a differential diagnostic problem when extending into the bladder, but in rare cases basal cell markers such 34ßE112 cytokeratin and p63, which are usually negative in prostate cancer, and PSA immunostaining may be helpful. Recently, it has been suggested that uroplakin II could be a marker for molecular diagnosis of nodal metastases from bladder cancer.[133]

Soft tissue tumors of the urinary bladder

These are all rare and have been described in small series and isolated case reports. Myofibroblastic proliferations, including the inflammatory myofibroblastic tumor and the postoperative spindle cell nodule, still represent a degree of uncertainty in terms of classification and differential diagnosis. Other rare benign lesions of the bladder include leiomyomas, hemangiomas, and neurofibromas, with other examples of soft tissue tumors rarely described. Differentiation of benign from malignant lesions is critical to avoid overly aggressive therapy. Malignant mesenchymal tumors of the urinary bladder include leiomyosarcoma, rhabdomyosarcoma, angiosarcoma, and malignant fibrous histiocytoma (undifferentiated sarcoma). Recognizing these spindle cell lesions and differentiating them from sarcomatoid carcinoma is important as they have differing prognostic as well as therapeutic implications.

Myofibroblastic proliferations

Inflammatory myofibroblastic tumor

Inflammatory myofibroblastic tumor (IMT) of the bladder (inflammatory pseudotumor, inflammatory pseudosarcomatous fibromyxoid tumor, nodular fasciitis, pseudosarcomatous myofibroblastic tumor, fibromyxoid pseudotumor, and inflammatory myofibroblastic tumor)[150,151] was initially described as a lesion showing spindle cells in a myxoid stroma with scattered chronic inflammation (Figure 3.39). Typical mitoses were present but the lesion infiltrated the muscle. There was no recurrence after resection. Clinical presentation includes hematuria, abdominal pain, bladder mass, cystitis, or obstructive symptoms. Grossly, the lesion is either a polypoid mass or a submucosal nodule. The tumor may or may not cause surface ulceration and the cut surface is often pale, firm, and gelatinous.[150,151] At histology, there is a spindle cell proliferation with elongated eosinophilic cytoplasmic processes in a loose edematous or myxoid background. Nuclei may be large with occasional atypia. Single, prominent nucleoli may be identified. Occasional mitotic figures are seen, none of which is atypical; mitotic rates vary from 0 to 20 mitoses per 10 hpf (high-power field). Inflammation, usually chronic consisting of a lympho-plasmacytic infiltration, is seen.[150,151] Some lesions have eosinophils or neutrophils, which may be focally prominent. Extravasated red blood cells may be present. Three identifiable histologic patterns including the most common nodular fasciitis-like pattern with myxoid, vascular, and inflammatory areas, a fibrous-histiocytoma pattern with more compact spindle cell proliferation and scattered lymphocytes, plasma cells or eosinophils; and a scar or desmoid-like pattern with dense collagen have been reported.[150,151] Infiltration into the muscularis propria or even perivesical involvement may be seen in IMT. Typically, the lesion occurs in young patients, with a female predominance, ranging from 9 to 42 years of age. Tumor size ranges from 1.5 to 13 cm. Follow-up data of IMT have revealed no evidence of metastases, but the lesion may recur after surgery.[150,151]

Immunohistochemical reactivity has been variable, so it may or may not be helpful in differentiating IMT from other spindle cell lesions of the bladder (Table 3.5). Immunoreactivity of IMT for actin and vimentin is usually seen, although it may be focal. P53 staining is weak or absent in IMT and postoperative spindle cell nodule (PSCN) but strongly and diffusely positive in rhabdomyosarcoma and leiomyosarcoma or sarcomatoid carcinoma. Pancytokeratin reactivity, which may be patchy, is seen in many cases of IMT, but cytokeratin may be seen in other tumors such as leiomyosarcomas. Actin may not help differentiate benign from malignant tumors as alpha-smooth muscle actin (SMA) has been found positive in 43% of sarcomas, 63% of IMT, and an intermediate percentage of postoperative spindle cell nodule (PSCN). Rhabdomyosarcoma rarely expresses SMA but leiomyosarcoma often does. Iczkowski et al[150]
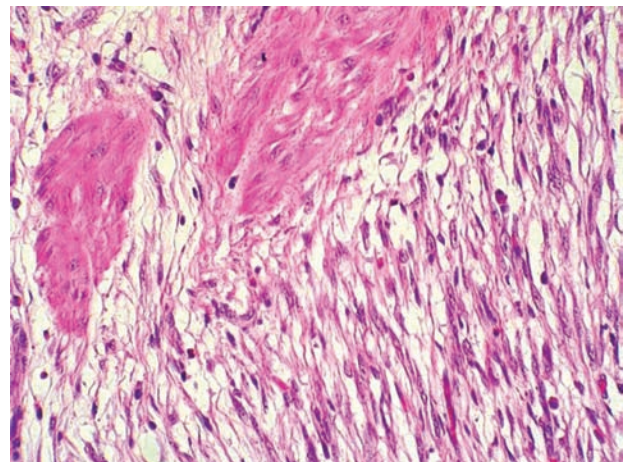

Figure 3.39
Inflammatory myofibroblastic tumor.

found three of 11 IMT, 2 of 3 PSCN, and 0 of 8 sarcomas were reactive for desmin, which may be present also in leiomyosarcoma. IMT shows variable staining for EMA. IMT is negative for myoglobin, whereas rhabdomyosarcoma often exhibits positive immunostaining for skeletal muscle markers such as myogenin or MyoD1. McKenney[152] states the strong coexpression of SMA and cytokeratin to be characteristic of vesical myofibroblasts.

The main differential diagnosis includes PSCN (described below), embryonal rhabdomyosarcoma, and leiomyosarcoma. The differentiation between IMT and PSCN is somewhat academic, as both are similar and are felt to represent the same process. PSCN reportedly is more likely to have eosinophils.[150,151] IMT can be confused with myxoid leiomyosarcoma since both may have a myxoid stroma. Morphologically, the leiomyosarcoma is more uniform in its cellularity with more cytologic atypia, while the IMT has a more prominent network of small blood vessels and more inflammatory infiltrates.[150,151] IMT may have necrosis at the site of surface ulceration and may infiltrate the detrussor muscle, but does not exhibit deep necrosis as may be seen in a sarcoma. However, in a recent series by Harik et al,[153] 32% of cases showed necrosis in the deep bladder wall, two of which were extensively necrotic. Recently, positive cytoplasmic immunostaining for anaplastic lymphoma kinase (ALK-1) has been identified in 89% of IMT in the bladder. The ALK-1 staining was confirmed by fluorescence in situ hybridization (FISH), with translocation of the ALK gene on chromosome 2p23 in some cases. It has been suggested that ALK negative cases have a lower chance of recurring.[133] Neither ALK-1 staining nor translocation of the ALK-1 gene was identified in any cases of bladder leiomyosarcoma or rhabdomyosarcoma. However, non-bladder spindle cell lesions may display ALK-1 expression in 40% of IMT, 19% of rhabdomyosarcomas, and 10% of leiomyosarcomas.

Harik et al[153] proposed that there is enough evidence to distinguish 'pseudosarcomatous myofibroblastic proliferations' of the bladder from IMT of childhood, which is often associated with systemic symptoms, such as fever and weight loss, as well as laboratory abnormalities, such as anemia, thrombocytosis, and polyclonal hypergammaglobulinemia.

Postoperative spindle cell nodule

Postoperative spindle cell nodule may be seen in both genders months after surgical instrumentation and is characterized by nodules up to 4 cm in size in the lower genital and lower urinary tract.[150–153] Patient age ranged from 29 to 79 years and the presenting symptoms included hematuria and obstruction, or just incidental finding. Microscopically the tumors were described as uniform, composed of intersecting fascicles of plump spindle cells with delicate vasculature, focal hyalinization, and moderate collagen in some. The spindle cells had abundant, tapering, eosinophilic cytoplasm. The nuclei varied only slightly in size. Numerous mitotic figures, ranging from 1 to 25 per 10 hpf, without evidence of atypia, were identified. All lesions had ulceration with acute inflammatory cells as well as scattered chronic inflammatory cells in deeper areas. The tumor had infiltrating margins with smooth muscle destruction. Moderate edema and small foci of hemorrhage were identified. There was no cytologic atypia. Follow-up revealed no recurrences or metastases; eosinophilia may be prominent. Immunohistochemical staining was positive for cytokeratin AE1/AE3, CAM5.2, and vimentin in some. Other cases were immunoreactive for vimentin only. Key to distinguishing these lesions from sarcoma was the lack of necrosis or myxoid degeneration, lack of nuclear atypia, lack of

metastatic potential, and predominance of chronic over acute inflammation. P53 was the only immunostain found to differentiate benign (rare reactive cells) from malignant (stronger, more diffuse reactivity) soft tissue tumors.[150–153] The differential diagnoses for PSCN include sarcomatoid carcinoma, myxoid leiomyosarcoma, rhabdomyosarcoma, and malignant fibrous histiocytoma (see IMT section for discussion). Harik et al[153] proposed that the PSCN and the inflammatory pseudotumor, which occurs without a history of surgical procedure, are indistinguishable and should be classified as 'pseudosarcomatous myofibroblastic proliferation'.

Benign soft tissue tumors

Leiomyoma

Although rare, leiomyoma is the most common benign neoplasm of the bladder (Figure 3.40). A review by Goluboff et al[154] of 37 cases reported that 59% occurred in the third through sixth decades, with an average patient age of 44 years. Seventy-six percent occurred in women. Presenting symptoms included obstructive symptoms (49%), irritative symptoms (38%), hematuria (11%), flank pain (13%), and asymptomatic (19%). Tumors were most often endovesical, followed by extravesical or intramural. Grossly, these tumors are typically small, well-circumscribed, white without hemorrhage or necrosis, and a tumor size of 1.6 to 5.8 cm. Microscopically, leiomyomas consist of intersecting fascicles of smooth muscle cells with moderate to abundant eosinophilic cytoplasm. They usually display only low cellularity without evidence of myxoid change. Nuclei are oval to cigar-shaped, centrally located, and blunt-ended. They are without significant nuclear atypia and without evidence of mitotic activity or necrosis. Examples of angioleiomyoma have been reported.
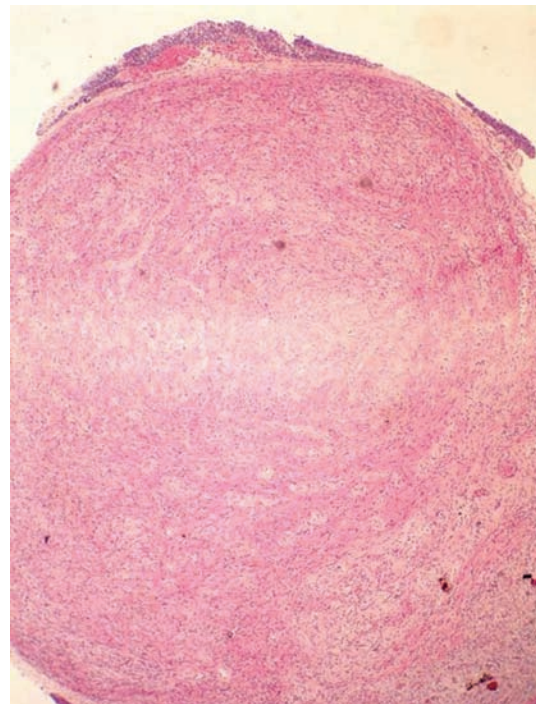

Figure 3.40
Submucosal leiomyoma.

Leiomyoma displays immunoreactivity for SMA, actin, desmin, and vimentin. Some may express CD34 but most are usually negative for cytokeratin and S-100 protein. Excision is usually curative.[154]

Hemangioma

The largest series of bladder hemangiomas to date includes 19 patients compiled by Cheng et al.[155] In this series the mean age at time of diagnosis was 58 years; previous reports indicated the lesion occurred in all age groups, but usually under age 30 years. Cheng reported a male:female ratio of 3.7:1. The usual presenting symptom is gross hematuria; other reported symptoms include irritative voiding and abdominal pain. Endoscopically, a sessile, blue, raised mass may be seen. These lesions are usually small (median 0.7 cm). Most often, hemangiomas are found on the posterior and lateral walls of the bladder. The most common type of hemangioma reported in the bladder is cavernous; much less frequent are capillary or arteriovenous types. Histologically, these lesions are identical to those at other sites. Effective conservative treatment consists of biopsy with or without fulguration. After such treatment, none of the 19 patients in Cheng's series developed recurrence (mean follow-up 6.9 years).[155] The differential diagnosis for bladder hemangioma includes angiosarcoma and Kaposi sarcoma, both of which exhibit more cytologic atypia. Exuberant granulation tissue contains prominent inflammation, which is not a significant feature of hemangioma. Multiple hemangiomas may be associated with syndromes predisposing to their development, including Klippel–Trenaunay–Weber and Sturge–Weber syndromes. Bladder hemangioma is a rare lesion with a favorable outcome.

Neurofibroma

Neurofibroma of the urinary bladder is rare; most occur in the setting of neurofibromatosis type 1 rather than as isolated lesions. Classically, neurofibromas of the urinary bladder occur in young patients with a slight male predominance, an average age at diagnosis of 17 years, and a male:female ratio of 1:1. Presenting symptoms include hematuria, irritative symptoms, and pelvic mass. Neurofibroma is a benign, probably neoplastic tumor of the nerve sheath. It consists of a proliferation of Schwann cells, perineurium-like cells, fibroblasts, and intermediate type cells. The histologic findings are the same as in neurofibromas of other organs. Classically, they present as hypocellular proliferation of spindle cells, loosely arranged into fascicles with scattered 'shredded carrot' bundles of collagen. Individual cells have wavy, bland nuclei. In the series by Cheng et al,[156] three of four were transmural with both diffuse and plexiform growth patterns. Another case had diffuse submucosal involvement with subepithelial pseudo-Meissnerian corpuscle formation on biopsy examination. Areas of diffuse involvement were hypocellular with small to medium sized spindle cells with ovoid to elongate nuclei in a collagenized matrix. A few mast cells were present. Immunohistochemical staining was reactive in all cases for S-100 protein as well as type IV collagen. Three were reactive for neurofilament protein in axons, and two neurofibromas expressed ALK-1 protein.[133] The differential diagnosis of bladder neurofibroma includes other spindle cell tumors such as leiomyoma, PSCN, inflammatory pseudotumor, low grade leiomyosarcoma, other nerve sheath tumors, and, rarely, rhabdomyosarcoma.[156]

Granular cell tumor

This tumor is rarely seen in the urinary bladder but cases reported occurred in adult patients 23 to 70 years of age. There is no gender predilection. They are usually solitary, well-circumscribed, and vary in size up to 12 cm. At histology, the cells have abundant granular eosinophilic cytoplasm and vesicular nuclei. S-100 protein can be identified in the tumor cells. A congenital granular cell tumor of the gingiva with systemic involvement including the urinary bladder has been reported. To date, only one malignant granular cell tumor of the bladder has been described.

Other benign soft tissue tumors

A solitary fibrous tumor of the urinary bladder has recently been recognized.[133] It occurs in older patients who present with pain or hematuria. Two of the seven cases that have been reported were incidental findings. The tumor is typically a polypoid submucosal mass. Histopathologic features include spindle cells arranged haphazardly in a variably collagenous stroma. Dilated vessels reminiscent of hemangiopericytoma are present. All solitary fibrous tumors of the bladder have had a benign course, although the number of cases is small, and follow-up has been short term in several cases. The proliferating cells typically express CD34 immunoreactivity. Paraganglioma (pheochromocytoma) has slight female predominance; it usually occurs in young patients (<50 years) and >80% of cases are functional with hematuria and hypertension during voiding. At cystoscopic examination, and biopsy, small (<3 cm), dome-shaped nodules covered by normal mucosa, usually located in the trigone or dome, are present. Histologically it is similar to paraganglioma of other body sites, with intact covering urothelium. Chromogranin is characteristically positive. Some urothelial carcinomas may mimic morphologically paraganglioma in transurethral resection specimens.[153–155]

Clear cell myomelanocytic tumor is a member of the family of perivascular epithelioid cell tumors. The one reported case arose from the muscularis propria of the urinary bladder in a 33-year-old woman. Clear to eosinophilic, epithelioid, and spindled cells arranged in fascicles or packets were a characteristic feature with delicate vascular stroma among the nests. Immunohistochemically it was positive for HMB-45 -and smooth muscle actin, and negative for S-100 protein, melan-A, desmin, and pan-cytokeratin. The patient was reported to be free of the disease 6 years following excision of the tumor.[156,157]

Malignant soft tissue tumors

Leiomyosarcoma

Leiomyosarcoma is the most common malignant mesenchymal tumor of the urinary bladder in adults[158,159] (Figure 3.41). It is very rare and ranges from 15 to 75 years of age, with the average age in the sixth to eighth decades. There is a male predominance. Presenting symptoms include gross hematuria, obstruction, dysuria, or abdominal mass. It is seen most often in the dome followed by the lateral walls. Several morphologic variants including myxoid and epithelioid have been described. Grossly, the tumor is large, unencapsulated,
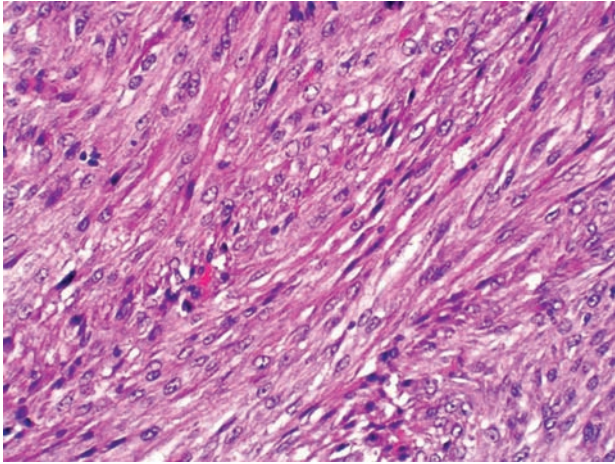
Figure 3.41
Bladder leiomyosarcoma.

and often polypoid, and exhibits invasive growth into all layers of the bladder. Usually leiomyosarcoma is firm or fleshy with a fibrous or myxoid appearance; some are hemorrhagic or necrotic, often with surface ulceration. At histology, there is significant nuclear pleomorphism with hyperchromasia and irregular nuclear membranes (usually readily identifiable at low power), tumor cell necrosis, increased mitotic activity, and infiltration of the muscularis propria. The majority of the tumors are moderately or well differentiated. Grading is based on the presence of cytologic atypia and mitotic activity: low-grade leiomyosarcoma (<5 mitoses per hpf), mild to moderate cytologic atypia, minimal necrosis, and an infiltrative margin; high-grade leiomyosarcoma as having moderate to marked cytologic atypia, with >5 mitoses per hpf and/or abundant necrosis. Grade seems to be determinant in prognosis.[158,159] Interlacing bundles and fascicles of elongated, eosinophilic cytoplasmic processes and spindled to elongate hyperchromatic nuclei are common. Highly pleomorphic, vesicular nuclei with macronucleoli and often bizarre mitotic figures, interspersed with some multinucleate giant cells, characterize high-grade lesions. Myxoid leiomyosarcoma may contain moderate numbers of thin-walled blood vessels, and epithelioid leiomyosarcoma has rounded tumor cells, which occasionally present clear and vacuolated cyotoplasm. Some leiomyosarcomas develop after the administration of cyclophosphamide and appear years after completion of therapy. Acrolein, a degradation product of cyclophosphamide, is thought to be the causative agent.[159]

Immunohistochemically, leiomyosarcomas usually stain positively for SMA (43–100%), vimentin, and desmin (0–60%). They are usually negative for epithelial markers including low molecular weight cytokeratins (CAM5.2, AE1/AE3) (10%+overall) and epithelial membrane antigen (5%+overall). ALK-1 immunostain is usually negative. Leiomyosarcoma must be differentiated from several other tumors including leiomyoma, sarcomatoid carcinoma, rhabdomyosarcoma, postoperative spindle cell tumor, or pseudosarcomatous myofibroblastic proliferations. Sarcomatoid carcinoma can be recognized by a history of a high-grade urothelial carcinoma or the presence of associated transitional in situ or invasive carcinoma. Therefore, extensive tissue sampling is recommended. Immunohistochemical staining in sarcomatoid carcinoma will be positive for low molecular weight cytokeratin and EMA. Sarcomatoid carcinoma immunostaining is usually negative for myogenous markers such as desmin and SMA, although it may be diffusely positive.

While leiomyosarcomas may show cytokeratin immunoreactivity, the pattern is usually focal or patchy.

Rhabdomyosarcoma may have a myxoid appearance but this tumor is extremely rare in adults. The presence of cross-striations and a cambium layer as well as positive staining for myogenin, both seen with rhabdomyosarcoma, can help differentiate these two tumors.[133,158,159]

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is infrequently seen in the urinary bladder in childhood and adolescence (Figure 3.42). Indeed, RMS is the most frequent malignant tumor of the bladder in children; there is a slight male predominance.[160] Children with neurofibromatosis type 1 have an increased prevalence of RMS with a predominance of bladder or prostate primaries. A handful of cases in the literature have described bladder RMS in adults. Although the prognosis in adults appears poor, there have been advances made in the treatment of childhood RMS leading to improved survival with preserved bladder function.

The classic presenting symptom for RMS is hematuria, but it may also present with an abdominal mass or obstructive symptoms. The most frequent site of involvement is adjacent to the trigone, an area which makes partial cystectomy difficult. Several histologic variants of RMS are seen in the bladder, with embryonal including the botryoid subtype being the most common. Grossly, RMS, including the sarcoma botryoides variant, often appears as a polypoid gelatinous and lobulated mass protruding into the bladder lumen, with variable hemorrhage and necrosis. Most tumors have a covering superficial epithelium. The botryoid embryonal RMS demonstrates a 'cambium' layer, or condensed layer of rhabdomyoblasts under the intact epithelium, under which may be a pauci-cellular myxoid tumor.[160] These areas may be admixed with more cellular areas and the tumor infiltrates deeply into the muscle wall. At histology, well-differentiated tumor cells (rhabdomyoblasts) may be small and elongated with frequent cross-striations, and have hyperchromatic nuclei. Less differentiated rhabdomyoblasts have been described as medium sized to large, irregularly shaped hyperchromatic nuclei with a small rim of cytoplasm and a high mitotic rate. Often atypical mitotic figures and bizarre cells are seen. Another rare variant reported to occur in the bladder is the alveolar RMS, which has closely packed
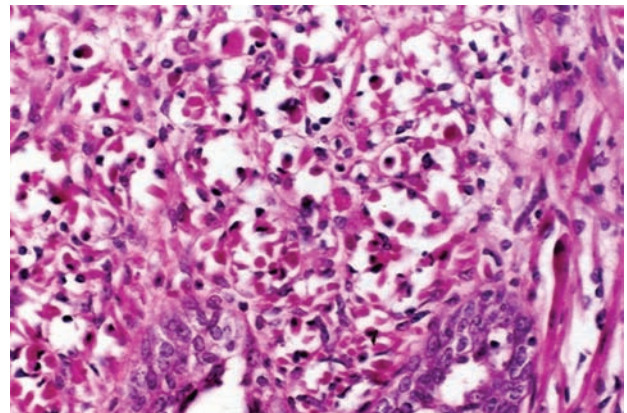

Figure 3.42
Bladder rhabdomyosarcoma.

alveolar spaces separated by thin fibrovascular septa lined by a single layer of cuboidal or polygonal hyperchromatic tumor cells in a hobnail pattern. Tumor cells floating in the alveolar spaces have also been described. The solid type of alveolar RMS grows in confluent sheets, but the cells are similar to those in the classic pattern. Mixed alveolar and embryonal types behave as an alveolar RMS. Interestingly, the botryoid subtype, which tends not to infiltrate deeply into the muscle, has an overall better prognosis than either deeply infiltrating endophytic embryonal tumors or the alveolar RMS. Immunohistochemical stains of RMS usually show positivity for desmin and MyoD1 or myogenin.[133] Also, muscle-specific actin, myoglobin, and myosin may be positive. Rhabdomyoblasts may stain for neuron-specific enolase and cytokeratin less frequently. The alveolar variant has been reported to stain focally with S-100. The differential diagnosis of bladder RMS includes IMT, leiomyosarcoma, neurofibroma, and sarcomatoid carcinoma. These tumors can often be distinguished on morphologic grounds.[160] A clinical history of a childhood tumor is helpful. Immunohistochemistry will often point towards muscle skeletal differentiation.

Angiosarcoma

Angiosarcoma of the bladder, which arises from blood vessel endothelium, is exceedingly rare and carries a very poor prognosis (70% of patients dying within 2 years of diagnosis). Angiosarcoma can arise in any part of the bladder and the age ranges from 38 to 85 years.[161] There is a male predominance. The development of angiosarcoma has been linked to certain environmental exposures including vinyl chloride, arsenic, and therapeutic irradiation. All cases have presented with hematuria. Other reported symptoms include flank or groin pain and dysuria. The disease has often extended locally beyond the bladder or metastasized at time of presentation. Frequent sites of metastases are lung and liver. Histologically, angiosarcoma of the bladder has been described as anastomosing vascular channels lined by atypical endothelial cells that often are pleomorphic with large hyperchromatic nuclei, prominent nucleoli, and mitoses. Lining cells may protrude into the lumen, imparting a hobnail appearance. There may be no intervening stroma. Vascular channels range in size from small capillaries to sinusoidal spaces.[161] A solid growth pattern of monomorphic (epithelioid) cells with vesicular chromatin and moderate eosinophilic cytoplasm arranged in sheets and nests has also been described; infiltration into the deep muscle layer may be present. Immunohistochemically, angiosarcoma stains positively for vimentin, CD31, and CD34.[133] The only reported epithelioid angiosarcoma of the bladder was negative for cytokeratins. The differential diagnosis for angiosarcoma of the bladder is hemangioma, which is usually small and lacks cytologic atypia, anastomosing channels, and solid areas. Kaposi sarcoma may be seen in the urinary bladder, especially in immunocompromised patients. Also in the differential is high-grade urothelial carcinoma.

Malignant fibrous histiocytoma (undifferentiated sarcoma)

Primary malignant fibrous histiocytoma (MFH) of the bladder is rare.[162] It occurs more commonly in men from 45 to 79 years of age, with gross hematuria at time of presentation. MFH consists of spindle and pleomorphic cells with a storiform pattern of growth (Figure 3.43).
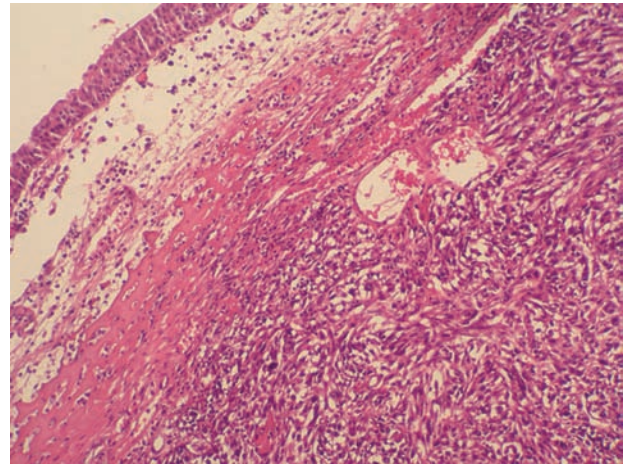

Figure 3.43
Malignant fibrous histiocytoma of the bladder.

The overlying urothelium may be normal or necrotic. The tumor is often large at presentation and involves all layers of the bladder wall. Four morphologic variants are recognized, including myxoid, inflammatory, storiform-fascicular, and pleomorphic.[162] Histologically, these tumors are composed of spindled or polygonal cells with variably sized oval to round nuclei displaying coarse chromatin and prominent nucleoli. Mitotic activity is moderate to high. Multinucleated giant cells are scattered throughout. In addition, many inflammatory cells, especially neutrophils have been identified between tumor cells in cases of inflammatory type MFH. Immunohistochemical stains can help differentiate MFH from other spindle cell neoplasms in the bladder. Typically, MFH is non-reactive for cytokeratin. It is often reactive for vimentin and alpha-1-antichymotrypsin, and focally reactive for CD68. Some tumors have reportedly stained strongly positive for neuron-specific enolase and S-100. Several tumors enter into the differential diagnosis of MFH.[133] Sarcomatoid carcinoma of the bladder may have a similar appearance, but an epithelial component immunoreactive to cytokeratin and EMA may be identifiable. Differentiating MFH from IMP or PSCN may be difficult. Mixed acute and chronic inflammatory cells and a history of a surgical procedure favor PSCN. MFH of the bladder is a highly aggressive tumor with a high local recurrence rate and frequent metastasis. Treatment is usually surgical with chemotherapy and radiation, but is often unsuccessful at inducing prolonged survival.

Osteosarcoma of the urinary tract

Defined as a malignant tumor showing osteoid production, osteosarcoma of the urinary bladder occurs in male patients 60–65 years of age. Some may follow earlier radiation therapy for urothelial carcinoma. Most osteosarcomas arise in the trigone region. Hematuria, dysuria, urinary frequency, and recurrent urinary tract infections are the most common presenting symptoms. Osteosarcoma of the urinary bladder most frequently presents as a solitary, large, polypoid, gritty, often deeply invasive, variably hemorrhagic mass. Tumor size is variable. Histologically, it is a high-grade, bone-producing sarcoma. Foci of chondrosarcomatous differentiation and/or spindle cell areas may also be observed. Variably calcified, woven bone lamellae are rimmed by malignant cells showing obvious cytologic atypia (as opposed to stromal osseous metaplasia occurring in some urothelial carcinomas). By definition, a recognizable malignant epithelial component should be absent, allowing discrimination

from carcinosarcoma, which is the most important differential diagnosis consideration.[125] Osteosarcoma of the urinary tract is an aggressive tumor with poor prognosis. A majority of patients have advanced stage at presentation and die of disease within 6 months. Lung metastases occur later in the course of the disease. The stage of the disease at time of diagnosis is the best predictor of survival.[125]

Other malignant soft tissue tumors arising in the bladder

Primary primitive neuroectodermal tumors (PNET) of the bladder are extremely rare and aggressive neoplasms[163] (Figure 3.44). Morphologic features correspond to a small, blue, round cell tumor without rosette formation and extensive areas of necrosis. Tumor cells show strong expression of CD99, vimentin, and CD 117 (c-kit), and focal reactivity to cytokeratin and S-100 protein. Ultrastructural study revealed sparse neurosecretory granules. Molecular genetic analysis supports the diagnosis of PNET by showing the EWS/FLI-1 fusion transcript type 2 by RT-PCR and EWS gene rearrangement by FISH (Figure 3.45). A patient treated with imatinib following systemic chemotherapy and radical surgery was still alive after 4 years' follow-up.[163]
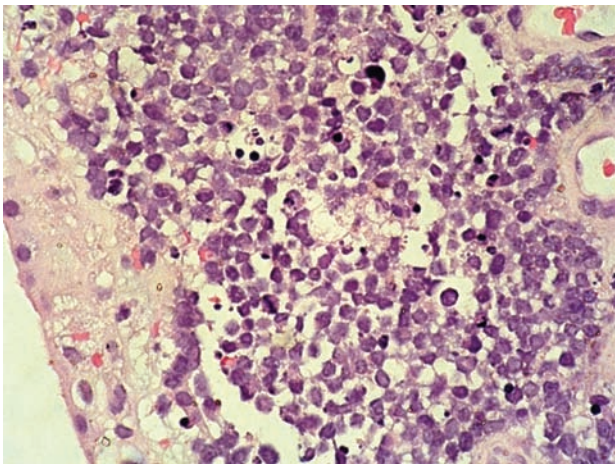
Figure 3.44
Primary primitive neuroectodermal tumor of the bladder.
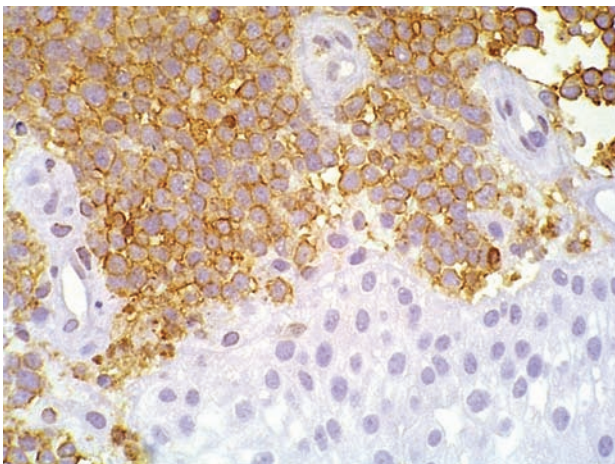
Figure 3.45
Primary primitive neuroectodermal tumor of the bladder, CD99 immunoreactivity.

Other malignant mesenchymal neoplasms such as malignant peripheral nerve sheath tumor, liposarcoma, chondrosarcoma, and Kaposi sarcoma very rarely involve the bladder. The diagnosis of primary liposarcoma and malignant peripheral nerve sheath tumor of the bladder requires that bladder involvement by direct extension from another site be excluded. In the case of primary bladder chondrosarcoma, sarcomatoid carcinoma must be excluded.[125] A single case of alveolar soft part sarcoma arising in the bladder has recently been reported.

Molecular pathology of bladder cancer

Molecular prognostic markers

An important question in clinical practice concerns the possibility of increasing the predictive value beyond staging, grading, and other classical prognostic factors by adding biomolecular markers. The topic has been and is under extensive investigation.[4,133] Three main fields are of urologic importance,[68] that is: (1) prognostic markers in superficial (Ta/T1) bladder tumors, (2) markers potentially helpful in selecting the best possible treatment for patients with invasive (T2–T4) bladder cancer, and of particular importance in selecting the appropriate precystectomy chemo/radiotherapy or targeted thaerapy, and (3) the clinical significance of studies using DNA/RNA array technology. It is hoped that this information can guide clinicians in future to predict response to presurgical systemic chemotherapy, irradiation, or other treatment modalities.[68]

Concerning prognostic markers in stage Ta/T1 tumors, a great number of new markers have been investigated in recent years. Although none of them can be recommended at present for routine use, these studies represent a substantial improvement in our knowledge of the disease. It is considered that p53 and tumor proliferation index are the most promising immunohistochemical markers.[23,69–71,135,164] However, after extensive investigation into the prognostic role of p53 over the last decade, evidence is not sufficient to conclude whether changes in p53 are valid markers of outcome in this subset of bladder tumors. Likewise, p53 has been a topic of considerable discussion. Meta-analysis results of over 3700 patients in 43 trials have shown that p53 correlates with tumor stage and grade, but it is unclear whether it has independent prognostic information.

Concerning tumor proliferation, markers such as ki-67 yield more promising results. Increasing evidence suggests that the high proliferation rate in bladder tumors can be used in defining more objectively pathologic grade of bladder tumors. In fact, a significant increase in proliferation rate in all categories of the 2004 WHO grading system can objectively establish risk categories.[23,69–71,135,164] However, the use of the ki-67 proliferation index for prognosis of bladder cancer awaits validation in prospective clinical studies. Cytokeratin 20 (CK20) is another marker for tumors of low stage and grade, and is expressed in the umbrella cells of normal urothelium and reactive atypia. When CK20 expression in bladder tumors is limited to the umbrella cells it is associated with a mild disease course, while expression in the entire urothelium in more than 10% of the tumor cells is associated with higher tumor grade and an increased risk of progression and recurrence. In urothelial carcinoma in situ, intense CK20 expression is found in the majority of malignant cells.

Another relevant issue actively under investigation is the question whether presently available biomarkers can guide uro-oncologists to

apply presurgical systemic chemotherapy.[23,69–71,135,164] At this point, a few clinical trials are ongoing with various chemotherapeutic regimens, mainly using p53, epidermal growth factor receptor (EGFr), tumor proliferation rate, p16, pRb, or HER2/neu. Whereas p53 dysfunction is clearly associated with a poor prognosis, it remains unclear precisely how tumors harboring TP53 mutations respond to radiotherapy and chemotherapy. On the one hand, reports indicate that urothelial tumors with functional p53 undergo apoptosis more readily and respond more favorably to chemotherapeutic agents and radiotherapy than those with a mutant p53. On the other hand, evidence indicates that patients with p53 alterations are more responsive to DNA-damaging agents, such as cisplatin and doxorubicin, and survive longer after adjuvant chemotherapy than patients with wild-type p53, a finding of clinical relevance. Some multicenter chemotherapy trials based on the status of p53 in bladder cancer are underway, and should help resolve this important issue. These studies are best considered as promising research investigations, but none of them can be recommended at present for routine use.[23,69–71,135,164,165]

Concerning the use of DNA arrays as prognosticators in bladder cancer, studies at the present time are limited, but some reports reach over 70% correct classification of bladder tumors in terms of prognostic grouping of patients, and therefore it should be considered a promising research tool.[26,166] Gene expression profiling by DNA microarray analysis ('gene chips') has provided new insights into the biology of bladder carcinoma and has been proposed as a new tool for the prediction of disease outcome.

Gene-chip studies have demonstrated that urothelial carcinoma can be clustered into different tumor stages and grades based on the overall gene expression profile alone. Several gene clusters that characterize superficial or invasive tumors have been identified. Superficial tumors, in general, showed increased expression levels of genes involved in protein synthesis and metabolism as well as of several genes involved in cell-cycle progression. Expression levels of genes that regulate the immune system, cell adhesion, extracellular matrix, remodeling, and angiogenesis were associated with muscle invasion and tumor progression. By the application of statistical analyses, cytokeratin 20, neuropilin-2, p21 (WAF1), and p33ING1 were identified as the top-ranked molecular markers linked to patient survival.[26,166–168]

Further analysis by immunohistochemistry demonstrated that cytokeratin 20 and neuropilin-2 were associated with tumor grade and stage. Furthermore, multivariate analysis revealed that high p33ING1 expression was linked to poor patient survival. Finally, two proteins, caveolin-1 and keratin 10, have been detected in early squamous metaplasia and squamous cell carcinoma of the bladder. It is known that squamous cell carcinoma is more resistant to radiotherapy and chemotherapy compared with conventional UC. Thus, the presence of those proteins before the morphologic identification of the squamous phenotype may aid in the selection of patients who can benefit from other therapeutic regimens.[26,166–168]

Molecular pathogenesis of early bladder cancer

Superficial (stage Ta or T1) bladder tumors have at least two pathways for development and progression which may explain the differences in the invasive and metastatic potential of the disease among specific cases.[26,30,166–169] Activation of the receptor tyrosine kinase (RTK)–Ras pathway and deletion of chromosome 9 are mainly responsible for the early development of papillary Ta superficial bladder tumors, which also includes mutation of fibroblast growth factor receptor 3 (FGFR3) in 60–70%, and of HRAS in 30–40% of cases. Partial or total deletion of chromosome 9 occurs in urothelial hyperplasia and low-grade papillary Ta tumors. Both 9q and 9p losses are involved in development of these neoplastic lesions. Indeed, a tumor suppressor gene may be located in the region at 9q32–33 (DBCCR1). In addition, it has been suggested that another tumor suppressor gene is located in the 9p21 region in the INK4A/ARF locus because the region encodes both p16 and p14. Homozygous deletion of this region downregulates both the RB and p53 pathways, which arrest cell-cycle progression. Furthermore, homozygous deletion at the p16INK4A/ARF locus is associated with superficial cancer having recurrent tumors of higher grade and larger size. Although chromosome 9 deletions were initially indicated to be early events in the development of low-grade Ta bladder tumors, they were subsequently revealed to participate in the development of high-grade cancer and, sometimes, of dysplasia and CIS. Mutations in the fibroblast growth factor receptor 3 (FGFR3) gene are very frequent in low-stage and low-grade urothelial tumors of the urinary bladder (about 75%). FGFR3 mutations occur less frequently in pT1G3 tumors, and are very rare in carcinoma in situ (pTis). Furthermore, patients with primary bladder cancers with an FGFR3 mutation were shown to have a significantly better prognosis than patients without a mutation. FGFR3-mutated pTa and pT1 tumors are therefore regarded as tumors with low malignant potential and a favorable prognosis.[26,30,166–169]

Increased proliferation activity using ki-67 immunohistochemistry (IHC) and TP53 mutations are both markers that indicate an unfavorable disease course. However, bladder tumors with an increased immunoreactivity for ki-67 and TP53 progress less often when an FGFR3 mutation is present. FGFR3 and TP53 were found to be almost mutually exclusive, suggesting that they both represent different pathways in bladder cancer development. The combination of FGFR3 mutation analysis and ki-67 IHC, defined as molecular grading, could be superior to histologic grading alone in the prediction of progression and survival of bladder cancer patients. Therefore, advances in the understanding of the pathogenesis of bladder cancer, such as mutations of the FGFr3 and HRAS genes, and deletions of several regions on chromosome 9 (not only in developed tumors but also in adjacent 'normal-looking' urothelium) might define a low-risk pathway for bladder tumors and represent a research topic for developing future therapeutic targets.[26,30,166–169]

Chromosomal abnormalities

Loss of heterozygosity (LOH) of chromosome 9 has attracted much attention because it is present during the earliest stages of urothelial tumorigenesis.[30,170–174] Independent methods such as cytogenetics, LOH analyses, comparative genomic hybridization (CGH), and array CGH consistently detect deletions of both arms of the chromosome in urothelial carcinomas. LOH of 9q is more prevalent in the low-grade, non-invasive papillary tumors than in CIS and invasive tumors. Both 9q and 9p losses are a hallmark of low-grade non-invasive papillary tumors and urothelial hyperplasia. Strikingly, even the normal-appearing urothelium that is adjacent to the tumor lesion harbors this chromosomal abnormality. However, Hartmann and colleagues found chromosome 9 deletions in both microdissected dysplastic urothelium and in CIS lesions, indicating that chromosome 9 deletions do not distinguish between the two

tumorigenesis pathways.[42,43] Nevertheless, another possibility is that the deleted regions harbor tumor suppressor genes. For instance, the cyclin-dependent kinase inhibitor 2A (CDKN2A) gene resides on 9p21 and encodes two alternatively spliced products, INK4A and ARF, which induce cell-cycle arrest through the retinoblastoma protein (RB) and p53 signaling pathways, respectively.[30,170–174] Although point mutations involving CDKN2A are rare in urothelial tumors, heterozygous and homozygous deletions of the gene are found in as many as 30–50% of these tumors. Functional inactivation of CDKN2A through methylation can also occur. Methylation of CpG islands of CDKN2A occurs in 67% of urothelial carcinoma specimens and this methylation correlates well with the absence of gene expression. Another candidate gene, termed tuberous sclerosis 1 (TSC1), resides on 9q34 and is found mutated in up to 12% of the urothelial tumors.[42,43,66] However, it remains unclear whether TSC1 defects contribute preferentially to one or the other of the urothelial tumorigenesis pathways.

Deletions that affect several other chromosomes are frequently found in urothelial carcinomas, indicating that other tumor-suppressor genes are involved. Of particular interest is the loss of 8p, which occurs in 25–30% of urothelial carcinomas and is primarily associated with high-grade and late-stage tumors.[30,170–174] Another example is the LOH of 15q, which occurs in about 40% of urothelial carcinomas. Further studies are required to determine whether the DNA repair gene RAD51, which is located at 15q15.1, functions as a tumor suppressor in urothelial carcinogenesis or tumor progression.[66]

Molecular bladder pathways and emerging therapies

Defining the genetic pathways of urothelial tumorigenesis provides a framework for devising rational, pathway-based therapies that will hopefully move beyond the current 'standard of care' therapies such as surgery, immunotherapy, chemotherapy, and radiotherapy. For example, the majority of low-grade, non-invasive papillary urothelial tumors have either HRAS or FGFR3 mutant proteins; therefore, inhibiting one or more component(s) of the RTK–Ras signaling pathway could have a therapeutic effect, minimizing the need for surgical intervention. Similarly, because over half of invasive urothelial tumors have deficiencies in the p53 and/or RB pathways, restoring these pathway functions could curb tumor growth, promote apoptosis, and prevent progression.[30,165–174]

Clonality analysis of multiple urothelial tumors

The development of multifocal tumors in either a synchronous or metachronous manner in the same patient is a common characteristic of this type of malignancy.[170–174] The multiple coexisting tumors have often arisen before clinical symptoms become apparent and the separate tumors may or may not share a similar histology. Two theories have been proposed to explain the frequent occurrence of urothelial tumor multifocality. One theory, the monoclonal theory, suggests that the multiple tumors are of monoclonal origin, arising from a single malignant transformed cell which proliferates and spreads throughout the urothelium either by intraluminal spread with secondary implantation at different sites within the urinary tract or by intra-epithelial migration.[170–174] The second theory, 'field-effect theory', explains tumor multifocality as developing secondary to a field-cancerization effect precipitated by carcinogens causing independent genetic alterations at different sites within the urothelial lining and leading to the development of multiple, genetically unrelated tumors. The issue of monoclonal versus oligoclonal origin of multifocal urothelial carcinomas is clinically important because an understanding of patterns of early tumor development must be considered in the development of appropriate treatment and surgical strategies and in the genetic detection of recurrent or residual tumor cells in post-treatment urine samples. There continues to be no consensus on which of the theories is most important in the development of multifocal urothelial carcinoma. Whereas many studies have suggested a monoclonal origin for multifocal urothelial carcinoma, other studies have clearly shown an independent origin for some multicentric urothelial tumors using a similar methodologic approach, that is microsatellite alterations and X-chromosome inactivation status in separate urothelial carcinomas from the same patients.[170–174]

Whereas the two theories are not mutually exclusive, it is unknown which mechanism is more important in leading to urothelial tumor multifocality. Detailed characterization and comparison of genetic alterations in the cells of separate tumors provides information about the clonal evolution of multifocal cancer. Loss of heterozygosity has been shown at various chromosomal loci in urothelial carcinomas. The chromosomal regions where LOH has been detected are thought to contain specific genes, the disruption of which leads to either neoplastic transformation or progression. Recently, evidence has been found for the independent origin of multifocal urothelial carcinomas in the majority of patients with multifocal urothelial carcinomas. The observation of many patients having two tumors with identical allelic loss patterns and a third or fourth tumor with a different LOH pattern provides evidence that both the monoclonal and field effect theories may be of importance in bladder carcinogenesis. Whereas tumor multifocality seems to be an oligoclonal phenomenon in the majority of cases, other studies do find support for the monoclonal hypothesis in some cases, therefore suggesting that both field-cancerization and monoclonal tumor spread may coexist in the same patient.[170–174]

References

1. Jemal A, Siegel R, Ward E et al. Cancer statistics, 2007. CA Cancer J Clin 2006; 57; 43–66.
2. Kirkali Z, Chan T, Manoharan M et al. Bladder cancer: epidemiology, staging and grading, and diagnosis. Urology 2005; 66 (Suppl 6A): 4–34.
3. Lopez-Beltran A, Montironi R. Non-invasive urothelial neoplasms: according to the most recent WHO classification. Eur Urol 2004; 46: 170–6.
4. Lopez-Beltran A, Sauter G, Gasser T et al. Urothelial tumors: infiltrating urothelial carcinoma. In: Eble JN, Sauter G, Epstein JI, Sesterhenn I, eds. World Health Organization Classification of Tumors: Pathology and Genetics of Tumors of the Urinary System and Male Genital Organs. Lyon: IARC Press, 2004.
5. Cheng L, Pan CX, Yang XJ et al. Small cell carcinoma of the urinary bladder: a clinicopathologic analysis of 64 patients. Cancer 2004; 101: 957–62.
6. Eble JN, Young RH. Carcinoma of the urinary bladder: a review of its diverse morphology. Semin Diagn Pathol 1997; 14: 98–108.
7. Fong A, Garcia E, Gwynn L et al. Expression of caveolin-1 and caveolin-2 in urothelial carcinoma of the urinary bladder correlates with

tumor grade and squamous differentiation. Am J Clin Pathol 2003; 120: 93–100.

8. Fossa S. Rare and unusual tumors of the genitourinary tract. Curr Opin Oncol 1992; 4: 463–8.

9. Cheng L, Neumann RM, Bostwick DG. Papillary urothelial neoplasms of low malignant potential. Clinical and biologic implications. Cancer 1999; 86: 2102–8.

10. Cheng L, Weaver AL, Neumann RM et al. Substaging of T1 bladder carcinoma based on the depth of invasion as measured by micrometer. A new proposal. Cancer 1999; 86: 1035–43.

11. Cheng L, Darson M, Cheville JC et al. Urothelial papilloma of the bladder. Clinical and biologic implications. Cancer 1999; 86: 2098–101.

12. Cheng L NR, Weaver AL, Spotts B et al. Predicting cancer progression in patients with stage T1 bladder carcinoma. J Clin Oncol 1999; 17: 3182–7.

13. Lopez-Beltran A, Cheng L, Andersson L et al. Preneoplastic non-papillary lesions and conditions of the urinary bladder: an update based on the Ancona International Consultation. Virch Arch 2002; 440: 3–11.

14. Lopez-Beltran A, Cheng L. Stage pT1 bladder carcinoma: diagnostic criteria, pitfalls and prognostic significance. Pathology 2003; 35: 484–91.

15. Sauter G, Algaba F, Amin M B et al. Non-invasive urothelial neoplasias. In: Eble JN, Sauter GS, Epstein JI, Sesterhenn I, eds.WHO Classification of Non-invasive Papillary Urothelial Tumors. World Health Organization Classification of Tumors: Pathology and Genetics of Tumors of the Urinary System and Male Genital Organs. Lyon: page 110 IARC Press, 2004.

16. Eble JN, Sauter G, Epstein JI et al. World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs. Lyon, France: IARC Press, 2004.

17. Cheng L, Weaver AL, Leibovich BC et al. Predicting the survival of bladder carcinoma patients treated with radical cystectomy. Cancer 2000; 88: 2326–32.

18. Cheng L, Cheville JC, Neumann RM et al. Natural history of urothelial dysplasia of the bladder. Am J Surg Pathol 1999; 23: 443–7.

19. Cheng L, Cheville JC, Leibovich BC et al. Survival of patients with carcinoma in situ of the urinary bladder. Cancer 1999; 85: 2469–74.

20. Lopez Beltran A, Bassi P, Pavone-Macaluso M et al. Handling and pathology reporting of specimens with carcinoma of the urinary bladder, ureter, and renal pelvis. Eur Urol 2004; 45: 257–66.

21. Palou J, Rodriguez-Rubio F, Huguet J et al. Multivariate analysis of clinical parameters of synchronous primary superficial bladder cancer and upper urinary tract tumor. J Urol 2005 Sep; 174(3): 859–61.

22. Droller MJ. Bladder cancer: state-of-the-art care. CA Cancer J Clin 1998; 48: 269–84.

23. Lopez-Beltran A, Luque RJ, Alvarez-Kindelan J et al. Prognostic factors in survival of patients with stage Ta and T1 bladder urothelial tumors: the role of G1-S modulators (p53, p21Waf1, p27Kip1, cyclin D1, and cyclin D3), proliferation index, and clinicopathologic parameters. Am J Clin Pathol 2004; 122: 444–52.

24. Malmstrom PU Buch C, Norlen BJ. Recurrence, progression, and survival in bladder cancer. A retrospective analysis of 232 patients with greater than or equal to 5-year follow-up. Scand J Urol Nephrol 1987; 21: 185–95.

25. Sylvester RJ, van der Meijden AP, Oosterlinck W et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol 2006; 49(3): 466–75.

26. Sanchez-Carbayo M, Socci ND, Lozano J et al. Defining molecular profiles of poor outcome in patients with invasive bladder cancer using oligonucleotide microarrays. J Clin Oncol 2006; 24(5): 778–89.

27. Reuter VE. The pathology of bladder cancer. Urology 2006; 67(3 Suppl 1): 11–17.

28. Mhawech-Fauceglia P, Cheney RT, Schwaller J. Genetic alterations in urothelial bladder carcinoma: an updated review. Cancer 2006; 106(6): 1205–16.

29. Kakizoe T. Development and progression of urothelial carcinoma. Cancer Sci 2006; 97(9): 821–8.

30. Hernandez S, Lopez-Knowles E, Lloreta J et al. Prospective study of FGFR3 mutations as a prognostic factor in nonmuscle invasive urothelial bladder carcinomas. J Clin Oncol 2006; 24(22): 3664–71.

31. Alsheikh A, Mohamedali Z, Jones E et al. Comparison of the WHO/ISUP classification and cytokeratin 20 expression in predicting the behavior of low-grade papillary urothelial tumors. World/Health Organization/International Society of Urologic Pathology. Mod Pathol 2001; 14: 267–72.

32. Alvarez Kindelan J, Lopez Beltran A, Anglada Curado F et al. Clinicopathologic differences between bladder neoplasm with low malignant potential and low-grade carcinoma. Actas Urol Esp 2001; 25: 645–50.

33. Schmitz-Drager BJ, van Roeyen CR, Grimm MO et al. P53 accumulation in precursor lesions and early stages of bladder cancer. World J Urol 1994; 12: 79–83.

34. Oosterlinck W, Solsona E, Akaza H et al. Low-grade Ta (noninvasive) urothelial carcinoma of the bladder. Urology 2005; 66 (6 Suppl 1): 75–8.

35. Bol M, Baak J, Buhr-Wildhagen S. Reproducibility and prognostic variability of grade and lamina propria invasion in stages Ta, T1 urothelial carcinoma of the bladder. J Urol 2003; 169: 1291–4.

36. Bostwick DG, Ramnani D, Cheng L. Diagnosis and grading of bladder cancer and associated lesions. Urol Clin North Am 1999; 26: 493–507.

37. Bostwick DG, Mikuz G. Urothelial papillary (exophytic) neoplasms. Virch Arch 2002; 441: 109–16.

38. Cordon-Cardo C, Cote RJ, Sauter G. Genetic and molecular markers of urothelial premalignancy and malignancy. Scand J Urol Nephrol 2000; Suppl: 82–93.

39. Dalbagni G HH, Reuter VE. Impact of a second transurethral resection on the staging of T1 bladder cancer. Urology 2002; 60: 822–4.

40. Esrig D FJ, Stein JP, Skinner DG Early cystectomy for clinical stage T1 transitional cell carcinoma of the bladder. Sem Urol Oncol 1997; 15: 154–60.

41. Epstein JI, Amin MB, Reuter VR et al. and 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: 1435–48.

42. Hartmann A, Moser K, Kriegmair M et al. Frequent genetic alterations in simple urothelial hyperplasias of the bladder in patients with papillary urothelial carcinoma. Am J Pathol 1999; 154: 721–7.

43. Hartmann A, Schlake G, Zaak D et al. Occurrence of chromosome 9 and p53 alterations in multifocal dysplasia and carcinoma in situ of human urinary bladder. Cancer Res 2002; 62: 809–18.

44. Harnden P, Eardley I, Joyce AD. Cytokeratin 20 as an objective marker of urothelial dysplasia. Br J Urol 1996; 78: 870–87.

45. Cheng L, Cheville JC, Neumann RM et al. Flat intraepithelial lesions of the urinary bladder. Cancer 2000; 88: 625–31.

46. Lopez-Beltran A, Luque RJ, Moreno A. The pagetoid variant of bladder urothelial carcinoma in situ. A clinicopathological study of 11 cases. Virch Arch 2002; 441: 148–53.

47. McKenney JK, Gomez JA, Desai S. Morphologic expressions of urothelial carcinoma in situ: a detailed evaluation of its histologic patterns with emphasis on carcinoma in situ with microinvasion. Am J Surg Pathol 2001; 25: 356–62.

48. Farrow GM UD. Observations on microinvasive transitional cell carcinoma of the urinary bladder. Clin Oncol 1982; 1: 609–14.

49. Jones TD, Cheng L. Papillary urothelial neoplasm of low malignant potential: evolving terminology and concepts. J Urol 2006; 175(6): 1995–2003.

50. Desai S, Lim SD, Jimenez RE et al. Relationship of cytokeratin 20 and CD44 protein expression with WHO/ISUP grade in pTa and pT1 papillary urothelial neoplasia. Mod Pathol 2000; 13: 1315–23.

51. Fujii Y, Kawakami S, Koga F et al. Long-term outcome of bladder papillary urothelial neoplasms of low malignant potential. BJU Int 2003; 92: 559–62.

52. Habuchi T, Ogawa O, Kakehi Y et al. Accumulated allelic losses in the development of invasive urothelial cancer. Int J Cancer 1993; 53: 579–84.

53. Holmang S, Andius P, Hedelin H et al. Stage progression in Ta papillary urothelial tumors: relationship to grade, immunohistochemical expression of tumor markers, mitotic frequency and DNA ploidy. J Urol 2001; 165: 1124–28; discussion 1128–30.

54. Holmang S, Johansson SL. Stage Ta-T1 bladder cancer: the relationship between findings at first followup cystoscopy and subsequent recurrence and progression. J Urol 2002; 167: 1634–7.

55. Jimenez RE, Keany TE, Hardy HT et al. pT1 Urothelial carcinoma of the bladder: criteria for diagnosis, pitfalls, and clinical implications. Adv Anat Pathol 2000; 7: 13–25.

56. McKenney JK, Amin MB, Young RH. Urothelial (transitional cell) papilloma of the urinary bladder: a clinicopathologic study of 26 cases. Mod Pathol 2003; 16: 623–9.

57. Montironi R, Scarpelli M, Mazzucchelli R et al. Subvisual changes in chromatin organization state are detected by karyometry in the histologically normal urothelium in patients with synchronous papillary carcinoma. Hum Pathol 2003; 34: 893–901.

58. Montironi R, Lopez-Beltran A, Mazzuchelli R et al. Classification and grading of the non-invasive bladder neoplasms: recent advances and controversies. J Clin Pathol 2003; 56: 91–5.

59. Mostofi FK, Sobin LH, Torloni H. Histological typing of urinary bladder tumours. Geneva: World Health Organization, 1973.

60. Murphy W. Editorial comment. J Urol 2001; 165: 1129.

61. Murphy WM, Takezawa K, Maruniak NA. Interobserver discrepancy using the 1998 World Health Organization/International Society of Urologic Pathology classification of urothelial neoplasms: practical choices for patient care. J Urol 2003; 168: 968–72.

62. Oosterhuis JW, Schapers RF, Janssen-Heijnen ML et al. Histological grading of papillary urothelial carcinoma of the bladder: prognostic value of the 1998 WHO/ISUP classification system and comparison with conventional grading systems. J Clin Pathol 2002; 55: 900–5.

63. Pich A, Chiusa L, Formiconi A et al. Biologic differences between noninvasive papillary urothelial neoplasms of low malignant potential and low-grade (grade 1) papillary carcinomas of the bladder. Am J Surg Pathol 2001; 25: 1528–33.

64. Reuter V. Bladder: risk and prognostic factors. A pathologist's perspective. Urol Clin North Am 1999; 26: 481–92.

65. Samaratunga H, Makarov DV, Epstein JI. Comparison of WHO/ISUP and WHO classification of noninvasive papillary urothelial neoplasms for risk of progression. Urology 2002; 60: 315–19.

66. Simon R, Jones PA, Sidransky D et al. Genetics and predictive factors of non-invasive urothelial neoplasias. In: Eble JN, Sauter G, Epstein JI, Sesterhenn I, eds. WHO Classification of Non-invasive Papillary Urothelial Tumors. World Health Organization Classification of Tumors: Pathology and Genetics of Tumors of the Urinary System and Male Genital Organs. IARCC Press, Lyon, France. 120–3.

67. Yorukoglu K, Tuna B, Dikicioglu E et al. Reproducibility of the 1998 World Health Organization/International Society of Urologic Pathology classification of papillary urothelial neoplasms of the urinary bladder. Virch Arch 2003; 443: 734–40.

68. Pavone-Macaluso M, Lopez-Beltran A, Aragona F et al. The pathology of bladder cancer: an update on selected issues. BJU Int 2006: 98: 1161–5.

69. Gonzalez-Campora R, Davalos-Casanova G, Beato-Moreno A et al. Apoptotic and proliferation indexes in primary superficial bladder tumors. Cancer Lett 2006; 242(2): 266–72.

70. Gonzalez-Campora R, Davalos-Casanova G, Beato-Moreno A et al. BCL-2, TP53 and BAX protein expression in superficial bladder cancer. Cancer Lett 2007; 250(2): 292–9.

71. Quintero A, Alvarez-Kindelan J, Luque RJ et al. Ki-67 MIB1 labelling index and the prognosis of primary TaT1 urothelial cell carcinoma of the bladder. J Clin Pathol 2006; 59(1): 83–8.

72. Montironi R, Lopez-Beltran A.The 2004 WHO classification of bladder tumors: a summary and commentary. Int J Surg Pathol 2005; 13(2): 143–53.

73. Scarpelli M, Montironi R, Tarquini LM et al. Karyometry detects subvisual differences in chromatin organisation state between non-recurrent and recurrent papillary urothelial neoplasms of low malignant potential. J Clin Pathol 2004; 57(11): 1201–17.

74. Bochner BH, Kattan MW, Vora KC et al. International Bladder Cancer Nomogram Consortium. Postoperative nomogram predicting risk of recurrence after radical cystectomy for bladder cancer. J Clin Oncol 2006; 24(24): 3967–72.

75. Fine SW, Humphrey PA, Dehner LP et al. Urothelial neoplasms in patients 20 years or younger: a clinicopathological analysis using the World Health Organization 2004 bladder consensus classification. J Urol 2005; 174(5): 1976–80.

76. Kruger S, Johannisson R, Kausch I et al. Papillary urothelial bladder carcinoma associated with osteoclast-like giant cells. Int Urol Nephrol 2005; 37(1): 61–4.

77. van Rhijn BW, Montironi R, Zwarthoff EC et al. Frequent FGFR3 mutations in urothelial papilloma. J Pathol 2002; 198: 245–51.

78. Sung MT, Maclennan GT, Lopez-Beltran A et al. Natural history of urothelial inverted papilloma. Cancer 2006; 107(11): 2622–7.

79. Lopez-Beltran A, Cheng L. Histologic variants of urothelial carcinoma: differential diagnosis and clinical implications. Hum Pathol 2006; 37(11): 1371–88.

80. Sung MT, Eble JN, Wang M et al. Inverted papilloma of the urinary bladder: a molecular genetic appraisal. Mod Pathol 2006; 19(10): 1289–94.

81. Amin MB, Gomez JA, Young RH. Urothelial transitional cell carcinoma with endophytic growth patterns: a discussion of patterns of invasion and problems associated with assessment of invasion in 18 cases. Am J Surg Pathol 1997; 21: 1057–68.

82. Guo CC, Fine SW, Epstein JI. Noninvasive squamous lesions in the urinary bladder: a clinicopathologic analysis of 29 cases. Am J Surg Pathol 2006; 30(7): 883–91.

83. Greene FL, Page DL, Fleming ID et al. AJCC Cancer Staging Manual. New York, Berlin, Heidelberg: Springer-Verlag, 2002.

84. Angulo JC LJ, Grignon DJ, Sanchez-Chapado M. Muscularis mucosae differentiates two populations with different prognosis in stage T1 bladder cancer. Urology 1995; 45: 47.

85. Bassi P, Ferrante GD, Piazza N et al. Prognostic factors of outcome after radical cystectomy for bladder cancer: a retrospective study of a homogeneous patient cohort. J Urol 1999; 161: 1494–7.

86. Dixon JS GJ. Histology and fine structure of the muscularis mucosae of the human urinary bladder. J Anat 1983; 136: 265–71.

87. Hasui Y OY, Kitada S, Nishi S. Significance of invasion to the muscularis mucosae on the progression of superficial bladder cancer. Urology 1994; 43: 782–6.

88. Holmang S HH, Anderstrom C, Holmberg E et al. The importance of the depth of invasion in stage T1 bladder carcinoma: a prospective cohort study. J Urol 1997; 157: 800–4.

89. Keep JC PM, Miller A, Oyashu R. Invasive carcinomas of the urinary bladder. Evaluation of the tunica muscularis mucosae involvement. Am J Clin Pathol 1989; 91: 575–9.

90. Miladi M PM, Zerbib M, Saighi D et al. The value of a second transurethral resection in evaluating patients with bladder tumors. Eur Urol 2003; 43: 241–5.

91. Platz CE CM, Jones MP, Olson DB et al. Is microstaging of early invasive cancer of the urinary bladder possible or useful? Mod Pathol 1996; 11: 1035–9.

92. Ro JY AA, el-Naggar A. Muscularis mucosa of urinary bladder. Importance for staging and treatment. Am J Surg Pathol 1987; 11: 668–73.

93. Sozen S AC, Sokmensuer C, Ekici S et al. Microstaging of pT1 transitional cell carcinoma of the bladder. Does it really differentiate two populations with different prognoses? (pT1 subcategory). Urol Int 2002; 69: 200–6.

94. Tosoni I, Wagner U, Sauter G et al. Clinical significance of interobserver differences in the staging and grading of superficial bladder cancer. BJU Int 2000; 85: 48–53.

95. van der Meijden A, Sylvester R, Collette L et al. The role and impact of pathology review on stage and grade assessment of stages Ta and T1 bladder tumors: a combined analysis of 5 European Organization for Research and Treatment of Cancer trials. J Urol 2000; 164: 1533–7.

96. Younes M SJ, True LD. The usefulness of the level of the muscularis mucosae in the staging of invasive transitional cell carcinoma of the urinary bladder. Cancer 1990; 66: 543–8.

97. Shen SS, Lerner SP, Muezzinoglu B et al. Prostatic involvement by transitional cell carcinoma in patients with bladder cancer and its prognostic significance. Hum Pathol 2006; 37(6): 726–34.

98. Kunju LP, Mehra R, Snyder M et al. Prostate-specific antigen, high-molecular-weight cytokeratin (clone 34betaE12), and/or p63: an optimal

immunohistochemical panel to distinguish poorly differentiated prostate adenocarcinoma from urothelial carcinoma. Am J Clin Pathol 2006; 125(5): 675–81.

99. Palapattu GS, Shariat SF, Karakiewicz PI et al. Bladder Cancer Research Consortium. Cancer specific outcomes in patients with pT0 disease following radical cystectomy. J Urol 2006; 175(5): 1645–9.

100. Schwaibold HE, Sivalingam S, May F et al. The value of a second transurethral resection for T1 bladder cancer. BJU Int 2006; 97(6): 1199–201.

101. Herr HW, Donat SM. A re-staging transurethral resection predicts early progression of superficial bladder cancer. BJU Int 2006; 97(6): 1194–8.

102. Reuter VE. Lymphovascular invasion as an independent predictor of recurrence and survival in node-negative bladder cancer remains to be proven. J Clin Oncol 2005; 23(27): 6450–1.

103. Lotan Y, Gupta A, Shariat SF et al. Lymphovascular invasion is independently associated with overall survival, cause-specific survival, and local and distant recurrence in patients with negative lymph nodes at radical cystectomy. J Clin Oncol 2005; 23(27): 6533–9.

104. Honma I, Masumori N, Sato E et al. Removal of more lymph nodes may provide better outcome, as well as more accurate pathologic findings, in patients with bladder cancer – analysis of role of pelvic lymph node dissection. Urology 2006; 68(3): 543–8.

105. Kassouf W, Leibovici D, Luongo T et al. Relevance of extracapsular extension of pelvic lymph node metastasis in patients with bladder cancer treated in the contemporary era. Cancer 2006; 107(7): 1491–5.

106. Lopez-Beltran A, Martin J, Garcia J et al. Squamous and glandular differentiation in urothelial bladder carcinomas. Histopathology, histochemistry and immunohistochemical expression of carcinoembryonic antigen. Histol Histopathol 1988; 3: 63–8.

107. Lopez-Beltran A, Requena MJ, Alvarez-Kindelan J et al. Squamous differentiation in primary urothelial carcinoma of the urinary tract as seen by Mac387 immunohistochemistry. J Clin Pathol 2007; 60(3): 332–5.

108. Sakamoto N, Tsuneyoshi M, Enjoji M. Urinary bladder carcinoma with a neoplastic squamous component: a mapping study of 31 cases. Histopathology 1992; 21: 135–41.

109. Drew PA, Furman J, Civantos F et al. The nested variant of transitional cell carcinoma: an aggressive neoplasm with innocuous histology. Mod Pathol 1996; 9: 989–94.

110. Holmang S, Johansson SL. The nested variant of transitional cell carcinoma – a rare neoplasm with poor prognosis. Scand J Urol Nephrol 2001; 35: 102–5.

111. Talbert ML, Young RH. Carcinomas of the urinary bladder with deceptively benign-appearing foci. A report of three cases. Am J Surg Pathol 1989; 13: 374–81.

112. Young RH, Zukerberg LR. Microcystic transitional cell carcinomas of the urinary bladder. A report of four cases. Am J Clin Pathol 1991; 96: 635–9.

113. Young RH, Oliva E. Transitional cell carcinomas of the urinary bladder that may be underdiagnosed. A report of four invasive cases exemplifying the homology between neoplastic and non-neoplastic transitional cell lesions. Am J Surg Pathol 1996; 20: 1448–54.

114. Amin MB, Ro JY, el-Sharkawy T et al. Micropapillary variant of transitional cell carcinoma of the urinary bladder. Histologic pattern resembling ovarian papillary serous carcinoma. Am J Surg Pathol 1994; 18: 1224–32.

115. Johansson SL, Borghede G, Holmang S. Micropapillary bladder carcinoma: a clinicopathological study of 20 cases. J Urol 1999; 161: 1798–802.

116. Amin MB, Ro JY, Lee KM et al. Lymphoepithelioma-like carcinoma of the urinary bladder. Am J Surg Pathol 1994; 18: 466–73.

117. Lopez-Beltran A, Luque RJ, Vicioso L et al. Lymphoepithelioma-like carcinoma of the urinary bladder: a clinicopathologic study of 13 cases. Virch Arch 2001; 438: 552–7.

118. Zukerberg LR, Armin AR, Pisharodi L et al. Transitional cell carcinoma of the urinary bladder with osteoclast-type giant cells: a report of two cases and review of the literature. Histopathology 1990; 17: 407–11.

119. Zukerberg LR, Harris NL, Young RH. Carcinomas of the urinary bladder simulating malignant lymphoma. A report of five cases. Am J Surg Pathol 1991; 15: 569–76.

120. Grammatico D, Grignon DJ, Eberwein P et al. Transitional cell carcinoma of the renal pelvis with choriocarcinomatous differentiation. Immunohistochemical and immunoelectron microscopic assessment of human chorionic gonadotropin production by transitional cell carcinoma of the urinary bladder. Cancer 1993; 71: 1835–41.

121. Martin JE, Jenkins BJ, Zuk RJ et al. Human chorionic gonadotrophin expression and histological findings as predictors of response to radiotherapy in carcinoma of the bladder. Virch Arch A Pathol Anat Histopathol 1989; 414: 273–7.

122. Oliva E, Amin MB, Jimenez R et al. Clear cell carcinoma of the urinary bladder: a report and comparison of four tumors of mullerian origin and nine of probable urothelial origin with discussion of histogenesis and diagnostic problems. Am J Surg Pathol 2002; 26: 190–7.

123. Jones EC, Young RH. Myxoid and sclerosing sarcomatoid transitional cell carcinoma of the urinary bladder: a clinicopathologic and immunohistochemical study of 25 cases. Mod Pathol 1997; 10: 908–16.

124. Lopez-Beltran A, Escudero AL, Cavazzana AO et al. Sarcomatoid transitional cell carcinoma of the renal pelvis. A report of five cases with clinical, pathological, immunohistochemical and DNA ploidy analysis. Pathol Res Pract 1996; 192: 1218–24.

125. Lopez-Beltran A, Pacelli A, Rothenberg HJ et al. Carcinosarcoma and sarcomatoid carcinoma of the bladder: clinicopathological study of 41 cases. J Urol 1998; 159: 1497–503.

126. Mahadevia PS, Alexander JE, Rojas-Corona R et al. Pseudosarcomatous stromal reaction in primary and metastatic urothelial carcinoma. A source of diagnostic difficulty. Am J Surg Pathol 1989; 13: 782–90.

127. Perret L, Chaubert P, Hessler D et al. Primary heterologous carcinosarcoma (metaplastic carcinoma) of the urinary bladder: a clinicopathologic, immunohistochemical, and ultrastructural analysis of eight cases and a review of the literature. Cancer 1998; 82: 1535–49.

128. Baydar D, Amin MB, Epstein JI. Osteoclast-rich undifferentiated carcinomas of the urinary tract. Mod Pathol 2006; 19(2): 161–71.

129. Parwani AV, Herawi M, Volmar K et al. Urothelial carcinoma with rhabdoid features: report of 6 cases. Hum Pathol 2006; 37(2): 168–72.

130. Bannach G, Grignon D, Shum D. Sarcomatoid transitional cell carcinoma vs pseudosarcomatous stromal reaction in bladder carcinoma: an immunohistochemical study. J Urol Pathol 1993; 1: 105–13.

131. Flamm J. Tumor-associated tissue inflammatory reaction and eosinophilia in primary superficial bladder cancer. Urology 1992; 40: 180–5.

132. Lipponen PK, Eskelinen MJ, Jauhiainen K et al. Tumour infiltrating lymphocytes as an independent prognostic factor in transitional cell bladder cancer. Eur J Cancer 1992; 29A: 69–75.

133. Emerson RE, Cheng L. Immunohistochemical markers in the evaluation of tumors of the urinary bladder: a review. Anal Quant Cytol Histol 2005; 27(6): 301–16.

134. Cai T, Nesi G, Boddi V et al. Prognostic role of the tumor-associated tissue inflammatory reaction in transitional bladder cell carcinoma. Oncol Rep 2006; 16(2): 329–34.

135. Lopez-Beltran A, Luque RJ, Alvarez-Kindelan J et al. Prognostic factors in stage T1 grade 3 bladder cancer survival: the role of G1-S modulators (p53, p21Waf1, p27kip1, cyclin D1, and cyclin D3) and proliferation index (ki67-MIB1). Eur Urol 2004; 45: 606–12.

136. Pagano F GA, Milani C, B assi P et al. Prognosis of baldder cancer I. Risk factors in superficial transitional cell carcinoma. Eur Urol 1987; 13: 145–9.

137. Grignon DJ, El-Bolkainy MN, Schmitz-Drager BJ et al. Squamous cell carcinoma. In: Eble JN, Sauter G, Epstein JI, Sesterhenn I eds. World Health Organization Classification of Tumors. Pathology and Gentics of Tumors of the Urinary System and Male Genital Organs. Lyon, France: IARC; 2004.

138. Grignon D, El-Bolkainy MN. Verrucous squamous cell carcinoma. In: Eble JN, Sauter G, Epstein JI, Sesterhenn I, eds. World Health Organization Classification of Tumors. Pathology and Gentics of Tumors of the Urinary System and Male Genital Organs. Lyon, France: IARC; 2004, pages 124–7.

139. Bentley G, Grignon D. Non-transitional epithelial tumors. In: Foster, Ross, eds. Pathology of the Urinary Bladder. MPP 42 series. Philadelphia, PA: Saunders, 2004.

140. Ayala AG, Tamboli P, El-Bolkainy MN et al. Adenocarcinoma. In: Eble JN, Sauter G, Epstein JI, Sesterhenn I, eds. World Health Organization Classification of Tumors. Pathology and Gentics of Tumors of the Urinary System and Male Genital Organs. Lyon, France: IARC; 2004.

141. Lopez-Beltran A, Luque RJ, Quintero A et al. Hepatoid adenocarcinoma of the urinary bladder. Virch Arch 2003; 442: 381–7.

142. Bollito ER, Pacchioni D, Lopez-Beltran A et al. Immunohistochemical study of neuroendocrine differentiation in primary glandular lesions and tumors of the urinary bladder. Anal Quant Cytol Histol 2005; 27(4): 218–24.

143. Suttmann H, Holl-Ulrich K, Peter M et al. Mesonephroid adenocarcinoma arising from mesonephroid metaplasia of the urinary bladder. Urology 2006; 67(4): 846–8.

144. Hartmann A, Junker K, Dietmaier W et al. Molecular evidence for progression of nephrogenic metaplasia of the urinary bladder to clear cell adenocarcinoma. Hum Pathol 2006; 37(1): 117–20.

145. Iqbal MA, Lawatsch EJ, Coyle DJ et al. Signet-ring cell carcinoma of the urinary bladder mimicking retroperitoneal fibrosis. WMJ 2006; 105(3): 55–8.

146. Lopez-Beltran A, Nogales F, Donne CH et al. Adenocarcinoma of the urachus showing extensive calcification and stromal osseous metaplasia. Urol Int 1994; 53: 110–13.

147. Cheng L, Jones TD, McCarthy RP et al. Molecular genetic evidence for a common clonal origin of urinary bladder small cell carcinoma and co-existing urothelial carcinoma. Am J Pathol 2005; 166(5): 1533–9.

148. Jones TD, Kernek KM, Yang XJ et al. Thyroid transcription factor 1 expression in small cell carcinoma of the urinary bladder: an immunohistochemical profile of 44 cases. Hum Pathol 2005; 36(7): 718–23.

149. Bates AW, Baithun SI. The significance of secondary neoplasms of the urinary and male genital tract. Virch Arch 2002; 440: 640–7.

150. Iczkowski KA, Shanks JH, Gadaleanu V et al. Inflammatory pseudotumor and sarcoma of urinary bladder: differential diagnosis and outcome in thirty-eight spindle cell neoplasms. Mod Pathol 2001; 14: 1043–51.

151. Lopez-Beltran A, Lopez-Ruiz J, Vicioso L. Inflammatory pseudotumor of the urinary bladder. A clinicopathological analysis of two cases. Urol Int 1995; 55: 173–6.

152. McKenney JK. An approach to the classification of spindle cell proliferations in the urinary bladder. Adv Anat Pathol 2005; 12(6): 312–23.

153. Harik LR, Merino C, Coindre JM et al. Pseudosarcomatous myofibroblastic proliferations of the bladder: a clinicopathologic study of 42 cases. Am J Surg Pathol 2006; 30(7): 787–94.

154. Goluboff ET, O'Toole K, Sawczuk IS. Leiomyoma of bladder: report of case and review of literature. Urology 1994; 43(2): 238–41.

155. Cheng L, Nascimento AG, Neumann RM et al. Hemangioma of the urinary bladder. Cancer 1999; 86: 498–504.

156. Cheng L, Scheithauer BW, Leibovich BC et al. Neurofibroma of the urinary bladder. Cancer 1999; 86: 505–13.

157. Pan CC, Yu IT, Yang AH et al. Clear cell myomelanocytic tumor of the urinary bladder. Am J Surg Pathol 2003; 27: 689–92.

158. Mills SE, Bova GS, Wick MR et al. Leiomyosarcoma of the urinary bladder. A clinicopathologic and immunohistochemical study of 15 cases. Am J Surg Pathol 1989; 13(6): 480–9.

159. Pedersen-Bjergaard J, Jonsson V, Pedersen M et al. Leiomyosarcoma of the urinary bladder after cyclophosphamide. J Clin Oncol 1995; 13(2): 532–3.

160. Leuschner I, Harms D, Mattke A et al. Rhabdomyosarcoma of the urinary bladder and vagina: a clinicopathologic study with emphasis on recurrent disease: a report from the Kiel Pediatric Tumor Registry and the German CWS Study. Am J Surg Pathol 2001; 25(7): 856–64.

161. Engel JD, Kuzel TM, Moceanu MC et al. Angiosarcoma of the bladder: a review. Urology 1998; 52(5): 778–84.

162. Egawa S, Uchida T, Koshiba K et al. Malignant fibrous histiocytoma of the bladder with focal rhabdoid tumor differentiation. J Urol 1994; 151(1): 154–6.

163. Lopez-Beltran A, Perez-Seoane C, Montironi R et al. Primary primitive neuroectodermal tumour of the urinary bladder: a clinico-pathological study emphasising immunohistochemical, ultrastructural and molecular analyses. J Clin Pathol 2006; 59(7): 775–8.

164. Malats N, Bustos A, Nascimento CM et al. P53 as a prognostic marker for bladder cancer: a meta-analysis and review. Lancet Oncol 2005; 6(9): 678–86.

165. Lopez-Beltran A, Requena MJ, Luque RJ et al. Cyclin D3 expression in primary Ta/T1 bladder cancer. J Pathol 2006; 209(1): 106–13.

166. Zieger K, Dyrskjot L, Wiuf C et al. R. Role of activating fibroblast growth factor receptor 3 mutations in the development of bladder tumors. Clin Cancer Res 2005; 11(21): 7709–19.

167. Knowles MA. Molecular subtypes of bladder cancer: Jekyll and Hyde or chalk and cheese? Carcinogenesis 2006; 27(3):361–73.

168. Lindgren D, Liedberg F, Andersson A et al. Molecular characterization of early-stage bladder carcinomas by expression profiles, FGFR3 mutation status, and loss of 9q. Oncogene 2006; 25(18): 2685–96.

169. Kitamura H, Tsukamoto T. Early bladder cancer: concept, diagnosis, and management. Int J Clin Oncol 2006; 11(1): 28–37.

170. Habuchi T. Origin of multifocal carcinomas of the bladder and upper urinary tract: molecular analysis and clinical implications. Int J Urol 2005; 12(8): 709–16.

171. Denzinger S, Mohren K, Knuechel R et al. Improved clonality analysis of multifocal bladder tumors by combination of histopathologic organ mapping, loss of heterozygosity, fluorescence in situ hybridization, and p53 analyses. Hum Pathol 2006; 37(2): 143–51.

172. Jones TD, Carr MD, Eble JN et al. Clonal origin of lymph node metastases in bladder carcinoma. Cancer 2005; 104(9): 1901–10.

173. Jones TD, Wang M, Eble JN et al. Molecular evidence supporting field effect in urothelial carcinogenesis. Clin Cancer Res 2005; 11(18): 6512–19.

174. Mazzucchelli R, Barbisan F, Stramazzotti D et al. Chromosomal abnormalities in macroscopically normal urothelium in patients with bladder pT1 and pT2a urothelial carcinoma: a fluorescence in situ hybridization study and correlation with histologic features. Anal Quant Cytol Histol 2005; 27(3): 143–51.

Section 4

Prostate cancer origins, diagnosis, and prognosis in clinical practice

Rodolfo Montironi, Roberta Mazzucchelli,
Antonio Lopez-Beltran, and Liang Cheng

Introduction

The incidence of prostate cancer (PCa) has risen dramatically in the past decade, probably owing to early detection programs that employ digital rectal examination, serum prostate-specific antigen, and transrectal ultrasonography.[1] In developed countries, PCa is the most commonly diagnosed non-skin malignancy in males.[1] It is estimated that 1 in 6 males will be diagnosed with PCa during their lifetime, the risk of death due to metastatic PCa being 1 in 30.[2] Multiple factors contribute to the development of PCa as well as to its progression to an androgen-independent state:[2] dietary factors, inherited susceptibility factors, gene defects, and androgens and their receptors.[3–5]

Part 1

Proposed preneoplastic lesions and conditions

Prostatic intra-epithelial neoplasia

Prostatic intra-epithelial neoplasia (PIN) refers to the pre-invasive end of the continuum of cellular proliferations within the lining of prostatic ducts, ductules, and acini. Initial references to such lesions were apparently made by Orteil,[6] Andrews,[7] and Kastendieck and Helpap,[8] but these authors did not distinguish these findings from mimics of PIN. In 1965, McNeal[9] emphasized the possible premalignant nature of proliferative changes in the prostatic epithelium, but his description included a variety of findings. Twenty-one years later, McNeal and Bostwick[10] described, for the first time, reproducible diagnostic criteria for the recognition of what they referred to as 'intraductal dysplasia', and introduced a three-grade classification system. The following year, Bostwick and Brawer[11] proposed the term of prostatic intra-epithelial neoplasia as a replacement for intraductal dysplasia, and this new term was promulgated in 1989 at a workshop on prostate preneoplastic lesions sponsored by the American Cancer Society and National Cancer Institute.[12] Terms such as intraductal dysplasia, severe dysplasia, large acinar atypical hyperplasia, duct–acinar dysplasia, and intraductal carcinoma are discouraged. The 1989 conference recommended compression of the PIN classification into two grades: low-grade (formerly PIN grade l) or high-grade PIN (formerly PIN grades 2 and 3) (HGPIN). The clinical significance of HGPIN was considered substantial at that time, whereas low-grade PIN was considered largely inconsequential.

Diagnostic criteria for HGPIN

The classification of PIN into low-grade and high-grade is chiefly based on the cytologic characteristics of the cells (Figures 4.1(A)–(C)). The nuclei of cells composing low-grade PIN are enlarged, vary in size, have a normal or slightly increased chromatin content, and possess small or inconspicuous nucleoli. HGPIN is characterized by cells with large nuclei of relatively uniform size, an increased chromatin content, which may be irregularly distributed, and prominent nucleoli that are similar to those of carcinoma cells. The basal cell layer is intact or rarely interrupted in low-grade PIN, but may have frequent disruptions in high-grade lesions. Although the cytologic features of low-grade and high-grade PIN are fairly constant, the architecture shows a spectrum varying from a flattened epithelium to a florid cribriform proliferation.

There are four main patterns of HGPIN: tufting, micropapillary, cribriform, and flat. The tufting pattern is the most common, present in 97% of cases, although most cases have multiple patterns. There are no known clinically important differences between the architectural patterns of HGPIN, and their recognition appears to be only of diagnostic utility. Other unusual patterns of HGPIN include the signet-ring cell pattern, small cell neuroendocrine pattern, mucinous pattern, and microvacuolated (foamy) pattern.[13,14] The presence of HGPIN with various histologic patterns provides additional support for a close relationship between HGPIN and the variants of invasive carcinoma of the prostate.[15]

There is inversion of the normal orientation of epithelial proliferation with HGPIN; proliferation predominately occurs in the basal cell compartment in the benign epithelium, whereas, in HGPIN, the greatest proliferation occurs on the luminal surface, similar to pre-invasive lesions in the colon (tubular adenoma) and other sites.

HGPIN spreads through prostatic ducts and ductules in multiple different patterns, similar to prostatic carcinoma. In the first pattern, neoplastic cells replace the normal luminal secretory epithelium, with preservation of the basal cell layer and basement membrane. This pattern often has a cribriform or near-solid appearance. Foci of HGPIN are usually indistinguishable from ductal spread of carcinoma by routine light microscopy; this was the main argument employed two decades ago to discard the terms 'intraductal dysplasia' and 'intraductal carcinoma' in the prostate. In the second pattern, neoplastic cells invaginate between the basal cell layer and columnar secretory cell layer ('pagetoid spread'), a very rare finding.[11]

HGPIN and cancer are usually multicentric.[16] HGPIN is multicentric in 72% of radical prostatectomies with cancer, including 63% of those involving the non-transition zone and 7% of those involving the transition zone; 2% of cases have concomitant single foci in all zones. The peripheral zone of the prostate, the area in which the majority of prostatic carcinomas occur (70%), is also the most common location for HGPIN. Cancer and HGPIN are frequently multicentric in the peripheral zone, indicating a 'field' effect similar to the multicentricity of urothelial carcinoma of the bladder.

Early stromal invasion, the earliest evidence of carcinoma, occurs at sites of acinar outpouching and basal cell disruption in acini with HGPIN (Figure 4.1(D)). Such microinvasion is present in about 2% of high-power microscopic fields of HGPIN, and is seen with equal frequency with all architectural patterns.[11,17,18] Foci of HGPIN associated with small cancers are lined by a crowded, pseudostratified epithelium, in contrast with the simple columnar or cuboidal lining of the malignant acini.[19] In some cases, a small tubular malignant acinus appears to originate abruptly from a dysplastic duct wall.[10,11,17–19]

Relationship of HGPIN to prostate cancer

Evidence linking HGPIN and prostate cancer has been found in morphologic, immunohistochemical, morphometric, molecular, and genetic studies.[20–22] Virtually all such studies have indicated that HGPIN is related more closely to prostate cancer than to benign epithelium.

Several authors have reported an increasing frequency of HGPIN with advancing age and its association with prostate cancer.
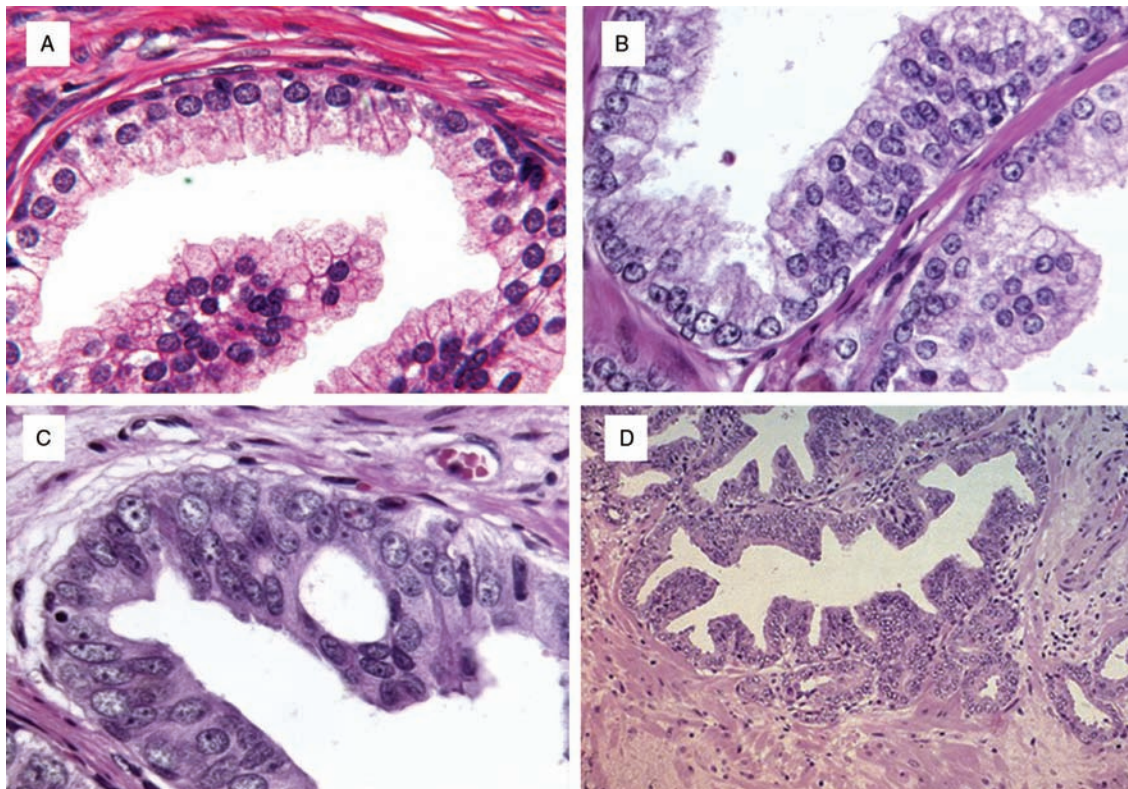
Figure 4.1
(A) Normal prostate; (B) low-grade PIN; (C) high-grade PIN; (D) high-grade PIN with early stroma invasion.

Bostwick and Brawer[11] demonstrated that the frequency of HGPIN in prostates with cancer is significantly increased when compared with prostates without cancer. McNeal and Bostwick[10] reported that HGPIN was present in 82% of step-sectioned autopsy prostates with cancer, but only in 43% of benign prostates from patients of similar age. Qian et al[23] found that 86% of whole-mount radical prostatectomy (RP) specimens with cancer contained HGPIN, usually within 2 mm of the cancer. The extent of HGPIN in prostates with cancer was also increased when compared with those without cancer. HGPIN was more extensive in small cancers than in larger cancers, presumably due to 'overgrowth' or obliteration of HGPIN by larger cancers.

The predominant location of HGPIN is the peripheral zone of the prostate where most cancers arise. The majority of foci of HGPIN are exclusively in the peripheral zone (or non-transition zone) (in one study, 63% of the cases) or simultaneously in the peripheral and transition zones (36%), and only rare cases (1%) are exclusively in the transition zone.[24–26] Other authors have reported a higher frequency of HGPIN in the transition zone, with a range of 2–37% of the cases.[26–29] Kovi et al[30] reported that the highest frequency of involvement of the transition zone (37%) was in prostatectomies with cancer, while this finding was significantly lower in studies of transurethral resection specimens.

Reproducibility in the diagnosis of HGPIN

Two studies have addressed the issue of interobserver and intraobserver variability in the identification of HGPIN.[31,32] Discrepancies between HGPIN and possible mimics fell into two main groups; one group included cases with prominent cytologic atypia without prominent nucleoli, whereas, in the other group, HGPIN was extensive or stood out at low magnification, but prominent nucleoli were not evident.

Discrepancies were greatest between HGPIN or cancer with cribriform proliferations.[32] The ductal pattern of carcinoma may have extensive necrosis or complex papillary fronds with fibrovascular cores, whereas these features are uncommon in HGPIN.

Other discrepancies arose in separating HGPIN and HGPIN with cancer.[32] HGPIN is occasionally associated with small acinar outpouchings or tangential sections which raise the important consideration of the minimum threshold for cancer. When the small atypical acini are too numerous and too crowded to be outpouchings or simply tangential sections, then cancer can be diagnosed. Immunohistochemical stains for the basal cell layer may be of some value, but reliance on negative staining for the diagnosis of cancer should only be made when the light microscopic findings are sufficiently compelling by themselves. HGPIN shows a discontinuous basal cell layer when labeled with the antibody to high-molecular-weight keratin, but benign glands may not always be labeled with this antibody. Allam et al[31] found that the variability in the identification of HGPIN was related to the level of expertise in prostatic pathology, the conditions of the study, the subjective applications of diagnostic criteria, and the influence of peers and clinical colleagues. These authors found that variability is linked to the fact that the cut-off point for HGPIN can vary within a certain range in the continuous spectrum of HGPIN. The management of the problems of translating descriptive terms into numerical values and of uncertainties in the diagnosis and grading of HGPIN has recently been addressed by Montironi et al.[33,34]

Effect of therapy on HGPIN

There is a marked decrease in the prevalence and extent of HGPIN in cases after androgen deprivation therapy and radiation therapy. (*See sections on pathologic changes after androgen manipulation and after radiation therapy.*)

Clinical significance

HGPIN is identified in 2–16.5% of needle biopsies. Its incidence probably varies according to the patient population under consideration (screening population vs urology office population). As an example, the American Cancer Society National Cancer Detection Project identified HGPIN and cancer in 5.2% and 15.8% men, respectively, from a series of 330 biopsies from men participating in an early detection project.[35] Lee et al[36] studied 256 ultrasound-guided biopsies of hypoechoic lesions in a urology practice setting, and identified HGPIN and cancer in 10.5% and 40.2% of patients. Interestingly, those with HGPIN had a mean age of 65 years, whereas those with cancer had a mean age of 70 years. HGPIN is encountered in up to 16.5% of contemporary needle biopsies in urology office practice.[37]

HGPIN has a high predictive value as a marker of adenocarcinoma, and its identification in biopsy specimens warrants further search for concurrent invasive carcinoma (Table 4.1). Davidson et al[38] found adenocarcinoma in 35% of subsequent biopsies from patients with a previous diagnosis of HGPIN, compared with 13% in a control group without HGPIN. HGPIN, patient age, and serum PSA concentration were all highly significant predictors of cancer, but HGPIN alone increased the risk 15-fold above those without HGPIN, and provides the highest risk ratio. Others have reported a high-predictive value of HGPIN for cancer, ranging from 38% to 100%.[39–47] Approximately 50% of men with HGPIN on biopsy will be found to have carcinoma on repeat biopsy within 2 years of follow-up. These data underscore the strong association of HGPIN and adenocarcinoma, and indicate that diagnostic follow-up is needed. Cancer detection rate in patients with low-grade PIN is identical to that in patients who underwent repeat biopsy for persistent elevated serum PSA or because of an abnormal digital rectal examination.[43,48]

Follow-up is suggested at 3- or 6-month intervals for 2 years, and thereafter at 12-month intervals for life. Identification of HGPIN in the prostate should not influence or dictate therapeutic decisions other than chemoprevention.

Table 4.1 Risk of detection of carcinoma on needle core rebiopsy

Initial diagnosis	Patients with cancer on rebiopsy (mean)
▪ Benign prostatic tissue	18.7%
▪ HGPIN	31.5%
▪ Atypical small acinar proliferation suspicious for malignancy	40.7%
▪ Atypical small acinar proliferation suspicious for malignancy + HGPIN	53%

Chemoprevention

Chemoprevention is the administration of agents to prevent induction of cancer, or to inhibit or delay its progression.[49] In prostatic neoplasia, the time from tumor initiation and progression to invasive carcinoma often begins in men in the fourth and fifth decades of life and extends across decades. This phenomenon represents a unique opportunity to arrest or reverse the process of carcinogenesis with the use of chemopreventive agents. For prostate cancer, as for other cancer targets, development of successful chemopreventive strategies requires suitable cohorts, reliable biomarkers for evaluating chemopreventive efficacy, and well-characterized agents.[49] Patients with isolated HGPIN in needle biopsies are considered one of the target populations for prostate cancer chemoprevention trials.

Intraductal carcinoma

Intraductal carcinoma is controversial as it has overlapping features with cribriform high-grade PIN and cannot be separated from intraductal spread of adenocarcinoma of the prostate.[50–52] The most salient morphologic feature distinguishing 'intraductal carcinoma' from high-grade cribriform PIN is the presence of multiple cribriform glands with prominent cytologic atypia containing comedo necrosis. In practice, this distinction rarely poses a problem in the evaluation of a prostatectomy specimen as invasive cancer is always concurrently present. In prostate needle biopsies and TURP, this process may rarely be present without small glands of adenocarcinoma, where some experts consider it prudent to refer to the lesion as high-grade cribriform PIN[52,53] with recommendation for repeat biopsy. Other experts will use the term 'intraductal carcinoma' on biopsy with the recognition that definitive therapy may be undertaken, recognizing that infiltrating cancer will be identified upon further prostatic sampling.[54]

Other proposed preneoplastic lesions and conditions

There are other possible findings in the prostate that may be premalignant, but the data for these are much less convincing than that for PIN.

Atypical adenomatous hyperplasia (adenosis)

Atypical adenomatous hyperplasia (AAH) is characterized by a circumscribed proliferation of closely packed small glands that, rather than appearing invasive, tends to merge with the surrounding, histologically benign glands[55] (Figures 4.2(A) and (B)). AAH frequently demonstrates budding acini from adjacent foci of benign hyperplastic glands, and the cells have clear cytoplasm with variable intraluminal secretions. Architecturally, AAH resembles well-differentiated adenocarcinoma, and most cases of Gleason primary pattern 1 cancer are now considered within the spectrum of AAH.[56] Recognition of the basal cell layer excludes the diagnosis of carcinoma. Unfortunately, identification of the basal epithelium is often difficult, as it is usually attenuated and may be discontinuous in AAH. Recognition of the
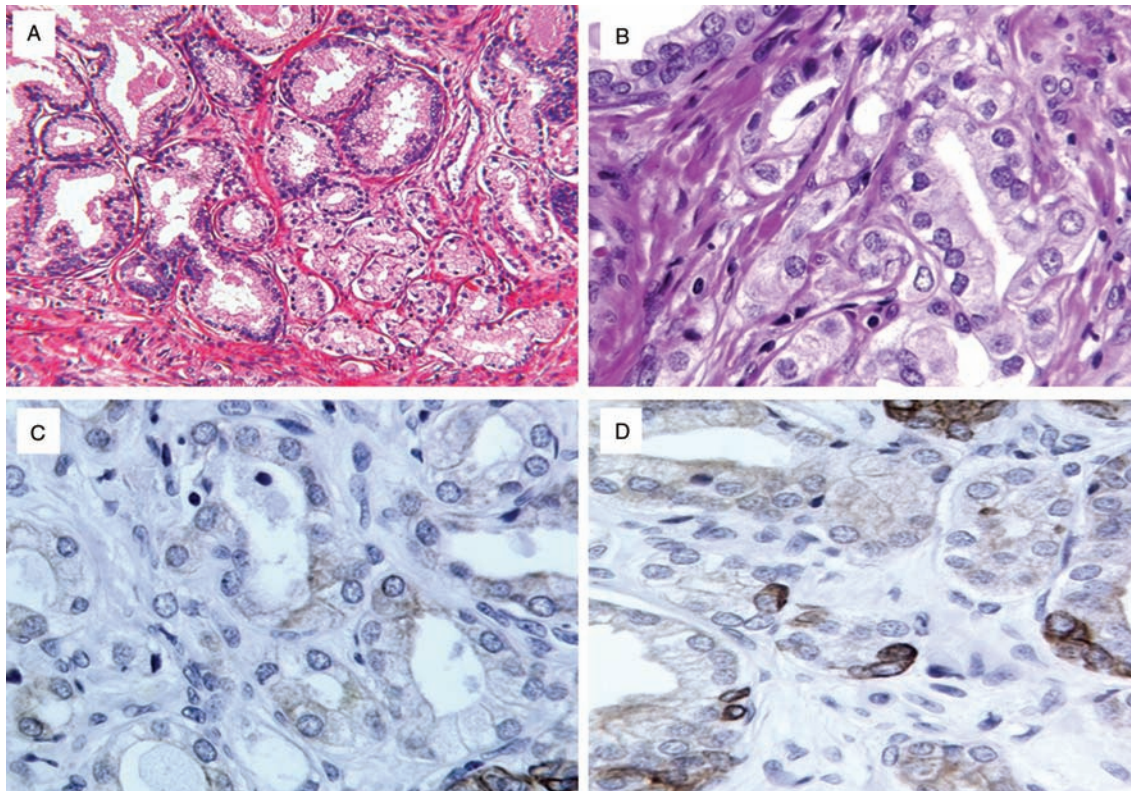
Figure 4.2
Atypical adenomatous hyperplasia (adenosis). (A) and (B) Circumscribed proliferation of closely packed small glands that, rather than appearing invasive, tends to merge with the surrounding, histologically benign glands. (C) and (D) Recognition of the basal cell layer may be facilitated by use of an antibody to high-molecular-weight cytokeratin (such as 34βE12).

basal cell layer may be facilitated by use of an antibody to high-molecular-weight cytokeratin (Figures 4.2(C) and (D)) or to p63 (see below). Nuclear and nucleolar morphology is the key differentiating feature between AAH and carcinoma. Cancer cells contain enlarged clear nuclei with a fine or irregular chromatin pattern and thick chromatinic rim. Most (86%) cases of AAH are located in the transition zone. The incidence of AAH in prostate specimens varies from 2.2% to 23%.[57,58]

AAH has been considered a premalignant lesion on the basis of several findings, including its increased incidence in association with carcinoma (15% in 100 prostates without carcinoma at autopsy, and 31% in 100 prostates with cancer at autopsy), topographic relationship with small-acinar prostate cancer, and rare cases with genetic abnormalities.[59] However, some authors claim that the link between cancer and AAH is an epiphenomenon and that the data are insufficient to conclude that AAH is a premalignant lesion. In particular, a direct transition from AAH to cancer, as has

been observed between PIN and cancer, has not been documented. The term adenosis is discouraged as it is not entirely synonymous with AAH.

Atrophy and cancer

Recent reports from one group suggest that atrophy, in particular post-inflammatory atrophy, may be causally linked to PIN and prostate cancer.[60] This hypothesis is based upon recognition of increased proliferative activity, albeit low, in the secretory cells that persist within atrophic acini. Autopsy studies of atrophy by McNeal in the 1960s rejected this concept, and the data supporting reconsideration at this time are limited.[a]

Part 2

Atypical small acinar proliferation suspicious for but not diagnostic of malignancy

An atypical focus suspicious for but not diagnostic of malignancy, also referred to as an atypical small acinar proliferation suspicious for but not diagnostic of malignancy, *is not a preneoplastic lesion.* It is descriptive diagnostic terminology used in the pathology report of a needle biopsy containing a small group of glands suspicious for adenocarcinoma, however with insufficient cytologic and/or architectural atypia to establish a definitive diagnosis.[61–66] It is a broad diagnostic 'umbrella' or category that encompasses benign lesions mimicking malignant glandular proliferations and undersampled, small foci of carcinoma that harbor some but not all of the features needed for a definitive diagnosis of malignancy.[61] It is not a diagnostic entity and is not synonymous with high-grade prostatic intraepithelial neoplasia (HGPIN).

A number of descriptive terms have been used to refer to a prostate tissue biopsy with a small focus of atypical glands. There are personal preferences and recommendations.[61,62,67] The term atypical small acinar proliferation suspicious for but not diagnostic of malignancy[63,65] has been adopted for many years in several laboratories throughout the world, including ours.

The acronym ASAP (it stands for atypical small acinar proliferation suspicious) has been commonly used to refer to atypical small acinar proliferation suspicious for but not diagnostic of malignancy. This term has been criticized and commented on.[68–70] In two recent consultation meetings[62,67] it was argued against the use of the term ASAP. The reasons included the equation by some urologists of the ASAP with HGPIN and because all of the atypical foci are not always 'small' acinar but may include glands with larger diameter.

Incidence and clinical features

An average of 5% of needle biopsy pathology reports show a diagnosis of atypical focus suspicious for but not diagnostic of malignancy (range 0.7 to 23.4%).[63,71–88] No clinical features are contributory to or predictive of atypical small acinar proliferations suspicious for malignancy.[63,65,66,72,78,89–91] The mean patient age is in the 60s, with a range of 40 to 95. The men are typically biopsied to rule out prostate cancer, with the clinical indication being an elevated PSA or abnormal digital rectal examination (DRE). The median PSA elevation usually is modest, ranging from 6 to 8 ng/ml, but very high PSA levels (>50 ng/ml) have been seen. Only few transrectal ultrasound results have been reported.[72]

Diagnostic implications

It encompasses a variety of lesions including benign mimickers of cancer and small foci of adenocarcinoma which, for a variety of reasons, cannot be accurately diagnosed[92] (Tables 4.2 and 4.3). It may be composed of acini of small size, i.e., smaller than normal ducts

---

Table 4.2 Differential diagnoses

Common
- Adenocarcinoma
- Atrophy
- Postatrophic hyperplasia
- Partial atrophy
- Basal cell hyperplasia
- Atypical adenomatous hyperplasia (adenosis)
- Inflammatory-associated atypia
- High-grade PIN

Less common
- Cowper's gland
- Nephrogenic metaplasia
- Clear cell cribriform hyperplasia
- Seminal vesicle/ejaculatory ducts
- Paraganglia
- Xantoma

Table 4.3 Factors resulting in the diagnosis of atypical small acinar proliferations suspicious for malignancy

Small size of focus
- Small number of acini in the focus of concern (invariably fewer than two dozen acini)
- Small focus size, average 0.4 mm in diameter
- Focus at core tip or biopsy edge, indicating that the focus is incompletely sampled
- Loss of focus of concern in deeper levels

Conflicting morphologic findings
- Distortion of acini raising concern for atrophy
- Lack of convincing features of cancer (insufficient nucleomegaly or nucleolomegaly)
- Clustered growth pattern mimicking a benign process such as atypical adenomatous hyperplasia
- Foamy cytoplasm raising concern for foamy gland carcinoma

Conflicting immunohistochemical findings
- Focally positive high molecular weight cytokeratin
- Focally positive p63 staining
- Negative racemase immunostain

Confounding findings
- Histologic artifacts such as thick sections or overstained nuclei
- Tangential cutting of adjacent high-grade PIN
- Architectural or cytologic changes (nucleomegaly and nucleolomegaly) owing to inflammation or other lesions

---

and acini, but may also include glands with a diameter similar to that of normal ducts and acini.[61]

Benign lesions mimicking malignant glandular proliferations considered to be problematic have changed over the years. In the past,

seminal vesicle tissue was considered one of the common mimickers of adenocarcinoma of the prostate.[93] Adenosis (Figure 4.2(B)) and complete atrophy (Figure 4.3(A)) have also been found to be common problems in previous years.[94] Contemporarily, partial atrophy is one of the most common benign mimickers of cancer.[95] In part the atypical diagnosis resulting from evaluation of partial atrophy relates to negative staining for high-molecular-weight cytokeratin, p63, and positive staining for racemase (see below).

As far as factors preventing a diagnosis of carcinoma are concerned, if carcinoma is marginally or imperfectly sampled the microscopic focus may be very small and contain only a small number of acini (Figure 4.3(B)). In some cases, the atypical focus is present only at the edge of the core or at its tip, where infiltration between benign acini cannot be appreciated. In these cases, if the glands do not show prominent cytologic and architectural atypia, a definite diagnosis of cancer may not be possible. Mechanical distortion from the needle biopsy can result in crush artifact of a few atypical glands and obscure cytologic detail. Problems with fixation and processing, especially with sections that are too thick or overstained, can also prevent definite diagnosis because of poor histologic detail. Prominent atrophy in or near a small focus of cancer confounds the diagnostic difficulty. A further confounding factor that hampers accurate interpretation is that not all cancers display all the classical features of malignancy. The absence of convincing cytologic features of malignancy and a clustered growth pattern can prevent a definite diagnosis in these cases. Prominent inflammatory change is common and can obscure cytologic features of a small focus of carcinoma and cause difficulty differentiating from reactive changes and distortion occurring in benign glands as a result of the inflammation.[92]

The combination of HGPIN and atypical small acinar proliferation suspicious for malignancy is found in 16 to 31% of cases[63,66,96] (Figure 4.3(C)). There are two distinct conditions where the two may occur.[64] The first is when there are discrete discontinuous foci of HGPIN and atypical foci suspicious for but not diagnostic of malignancy. The second is when a diagnosis of atypical foci results when there is definite HGPIN where one cannot distinguish small outpouchings or tangential sections of HGPIN from carcinoma associated with HGPIN.[97] In addition to these two conditions, HGPIN may involve small acini. This creates difficulty distinguishing it from cancer.[98]

Immunohistochemical findings

Basal cell immunostains

Immunostains such as p63[99] (nuclear stain) and high-molecular-weight cytokeratin that is detected by antibody 34βE12[100] (cytoplasmic stain) can aid in the investigation of atypical glandular proliferations by staining basal cells. Cancer lacks a basal cell layer, so the presence of basal cells in an atypical focus effectively excludes cancer from consideration (Figure 4.3(D)). Conversely, the absence of a basal cell layer in a small focus that is highly suspicious for cancer supports the diagnosis of cancer (Figure 4.3(E)). However, negative staining for basal cell markers is by itself not diagnostic of cancer,
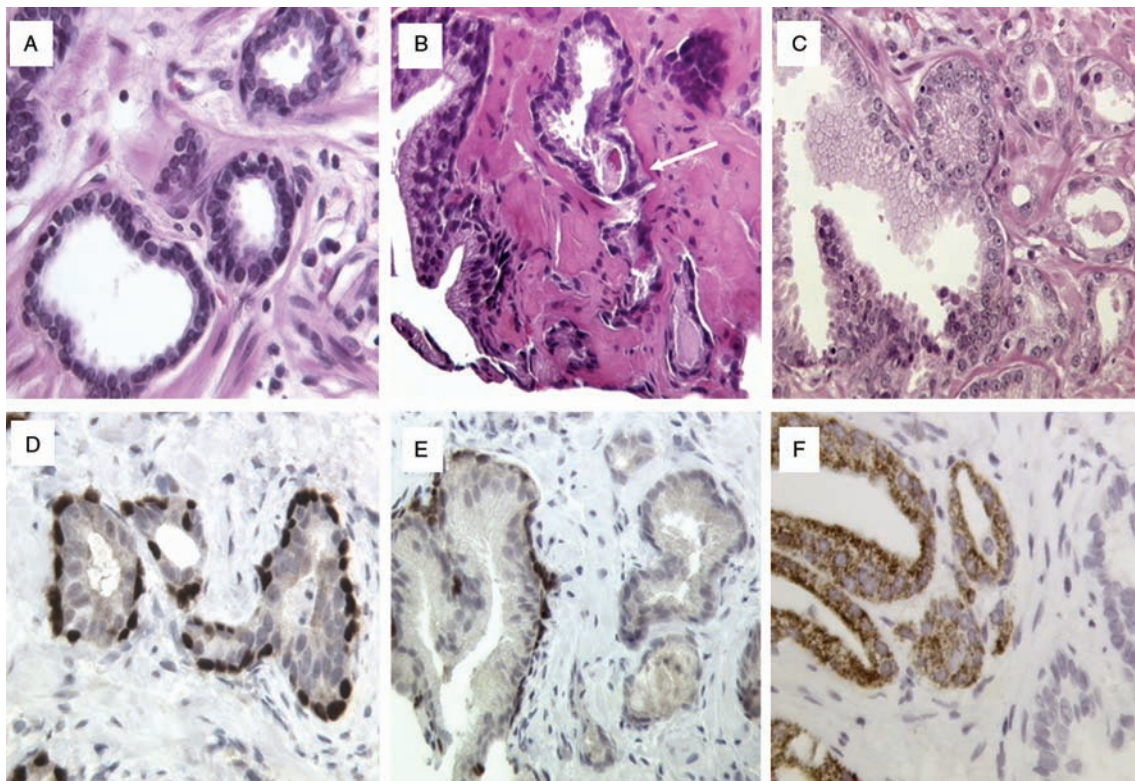
Figure 4.3
(A) Atypical focus, favor benign. (B) Atypical focus, highly suspicious for malignancy (arrow). (C) High-grade PIN with adjacent atypical focus. (D) p63 immunostaining of the basal cells in atrophy. (E) Atypical glands lack p63 immunostaining while a normal gland is positive (internal control). (The same case as in Figure 4.3(B). (F) AMACR immunostaining in atypical glands (negative glands serve as an internal control for normal).

as false-negative staining can arise from technical problems, including tissue changes induced by the surgical procedure (e.g., cautery artefact with transurethral resection of the prostate), imperfect specimen fixation, and variations in processing and antigen retrieval.[101] Negative staining should be interpreted only when there is confirmatory positive staining in adjacent benign glands. Staining variability with negative staining of benign glands, including atrophy and inflammation-associated changes, has also been reported.[102] Some benign lesions may have negative or discontinuous staining with basal cell markers.[57,102–104] In particular, fully developed atrophy typically stains fairly uniformly and intensely with basal cell markers whereas partial atrophy often has negative or discontinuous staining with these markers.[95] The combination of two basal cell stains (34βE12 + p63) increases the sensitivity of basal cell detection, compared with using either marker alone.[105,106] However, even with the combination of both these basal cell markers there are certain benign conditions and mimickers of cancer which will be negative.

Alpha-methylacyl-CoA racemase (AMACR)

Zhou et al found that racemase immunoreactivity converted atypical foci to cancer in approximately 10% of cases[107] (Figure 4.3(F)). The addition of racemase to keratin 34βE12 may allow a cancer diagnosis to be rendered in approximately 30%[92] of cases that might previously have been called atypical focus or HGPIN associated with it. Use of a p63/racemase cocktail resolved 87% of cases, more as cancer than as benign.[66,108,109]

Clinical significance

Predictive value for subsequent cancer

The risk of detection of carcinoma on needle core rebiopsy due to the presence in the initial biopsy of isolated atypical foci is reported in Table 4.1. The values range from 17 to 60%, the mean being 40.7%.[63,65,66,71,73,74,76,78,82,84,89–91,109,110]

Some decrease in predictive value for cancer has been claimed in some recent series.[66,84] For instance, Schlesinger et al found that isolated atypical foci have a predictive value of 37% for cancer; this is only a slight decrease from 45% observed between 1989 and 1996.[66] Various explanations have been put forward to explain such an observation: use of extended biopsy techniques, advances in immunostaining and previous PSA testing and biopsies in the same patient have been reported in some papers.[66,84]

Attempts have been made to place them into three tiers, such as favor benign, uncertain (or equivocal), and favor carcinoma (highly suspicious).[65,89,90] Such a stratification is not found to be significantly related to the risk of subsequent detection of carcinoma on rebiopsy. Even when a benign diagnosis is favored, up to 44% of patients (range 20 to 44%) are diagnosed with carcinoma on rebiopsy.[65,89,90,111,112] This three-tier stratification is not very reproducible, with 63% interobserver agreement in one study.[90,113]

Clinical parameters have limited predictive value for cancer on repeat biopsy.[114] Initial mean PSA concentration was higher in those with atypical foci suspicious for but not diagnostic of malignancy who had cancer in subsequent biopsies than in those whose subsequent biopsies were negative. Park et al reported that digital rectal examination and patient age were independent predictors of cancer in 45 patients with 'atypia';[91] conversely, other studies found that serum PSA and digital rectal examination findings were not predictive of cancer on subsequent biopsy.[66,109,115]

The mean cancer detection rate in patients who have an atypical focus and HGPIN is 53%, i.e., significantly higher than patients who have an isolated atypical focus.[116] A high frequency of cancer was observed by Leite et al. They found prostate cancer in 72.5% of men with HGPIN associated with an atypical focus in the initial biopsy.[115] Scattoni et al observed adenocarcinoma in 58% of repeat biopsies in patients with both lesions, whereas cancer was present in 35% with an isolated atypical focus in the initial biopsy.[109] These figures are similar to those reported by Kronz et al, who found that HGPIN with adjacent small atypical glands on prostate biopsy had a 46% follow-up cancer detection rate.[97] Conversely, Schlesinger et al reported that atypical small acinar proliferation associated with HGPIN predicted cancer in 33% of the cases, slightly lower than for atypical small acinar proliferations suspicious for malignancy alone (37%).[66]

The adenocarcinomas found on rebiopsy are mainly of intermediate grade, with Gleason scores of 5 and 6, but 30% are of high grade, with Gleason scores of 7 to 10.[89,90]

Of particular interest is the unique observation by Brausi et al who found that 100% of 25 patients with isolated atypical small acinar proliferations suspicious for malignancy who underwent prostatectomy had cancer.[73] This led those authors to suggest that immediate surgery was the treatment of choice for young patients with atypical small acinar proliferations suspicious for malignancy.

Rebiopsy strategy

Given the documented high risk of cancer in patients with atypical foci suspicious for but not diagnostic of malignancy, it is reasonable to consider rebiopsy within 3 to 4 months after an initial biopsy observation of atypical glands. Most carcinomas on rebiopsy are found within 6 months.[89,90]

It is intuitive that a greater diagnostic yield for malignancy will be provided by focusing on sites with documented atypical foci. However, the most useful repeat-biopsy strategy is controversial. Some authors recommend a sextant biopsy technique and additional biopsies directed to the site of atypical biopsy findings or to the ipsilateral site;[89] conversely, based on finding 85% of all cancers detected with repeat biopsies in the same sextant site, adjacent ipsilateral and adjacent contralateral sextant biopsies, Allen et al suggested rebiopsying to include several cores from the atypical location, two cores each from adjacent locations, and one each from other sextant locations.[117] Park et al calculated significant increased odds of finding cancer at the same site of atypical prostate biopsy: 65% probability, which increases to 88% when including adjacent sites.[91] On a multisite scheme study, Scattoni et al found precise spatial concordance between atypical small acinar proliferation and cancer in only 33% of the cases, similar to the likelihood of finding cancer in an adjacent site or in a non-adjacent site.[109]

Repeat biopsy results in a second diagnosis of atypical focus in about 6% of cases. These patients probably should undergo a second rebiopsy. Consideration for additional rebiopsy sessions probably should also be based on clinical findings (serum PSA and DRE results) and judgment.[65,78,89,118]

Part 3

Clinical features of prostate cancer

Signs and symptoms

Even before the serum prostate specific antigen test came into common usage, most prostate cancer was asymptomatic, detected by digital rectal examination. PSA screening has decreased the average tumor volume, and hence further lowered the percentage of cancers that present with symptoms today. Most cancers arise in the peripheral zone, so that transition zone enlargement sufficient to cause bladder outlet obstruction usually indicates hyperplasia.

Imaging

While the majority of early prostate cancers present as hypoechoic lesions in the peripheral zone on transrectal ultrasound imaging (TRUS), this sonographic appearance is non-specific, because not all cancers are hypoechoic and not all hypoechoic lesions are malignant.[119] Sonographic–pathologic correlation studies have shown that approximately 70–75% of cancers are hypoechoic and 25–30% of cancers are isoechoic and blend with surrounding tissues.[120,121] These cancers cannot be detected by TRUS. A small number of cancers are echogenic or contain echogenic foci within hypoechoic lesions.[122] The positive predictive value of a hypoechoic lesion to be cancer increases with the size of the lesion, a palpable abnormality in this region, and an elevated PSA level.[123] Overall the incidence of malignancy in a sonographically suspicious lesion is approximately 20–25%. To improve lesion detection the use of color Doppler US has been advocated, particularly for isoechoic lesions or to initiate a TRUS-guided biopsy which may not have been performed. Cross-sectional imaging techniques such as computed tomography and magnetic resonance imaging have not proven valuable because of low sensitivities to detect and stage prostate cancer.

Laboratory tests

Several laboratory tests are available for prostate cancer diagnosis. The test most used is prostate specific antigen (PSA) and its derivatives. PSA is elevated beyond the arbitrary cut-off point of 4.0 ng/ml in the majority of patients with prostate cancer. It may also be greater than 4.0 ng/ml in some benign conditions, including benign prostatic hyperplasia (BPH). Prostate cancer may also be present in men with serum PSA values lower than the above quoted cut-off points. This may be specifically true for men considered at higher risk (i.e., family history; men with faster doubling time; and in the United States African American men). Therefore, serum PSA lacks high sensitivity and specificity for PCa. This problem has been partially overcome by calculating several PSA-related indices and/or evaluating other serum markers.[124,125] The free form of PSA occurs to a greater proportion in men without cancer[126] and, by contrast, the α-1-chymotrypsin complex PSA comprises a greater proportion of the total PSA in men with malignancy. There is a significant difference in free-to-total PSA ratio between PCa and BPH patients with prostate volumes smaller than 40 cm^3, but not between patients in these two groups with prostate volumes exceeding 40 cm^3. The complex PSA value may offer better specificity than the total and free-to-total PSA ratio. Nodular hyperplasia is the main determinant of serum PSA levels in patients with BPH.[127–129] Therefore it seems logical that nodular hyperplasia volume rather than total volume should be used when trying to interpret elevated levels of serum PSA. PSA density of the transition zone is more accurate in predicting prostate cancer than PSA density for PSA levels of less than 10 ng/ml. It has been demonstrated that the rate of increase over time is greater in men who have carcinoma as compared to those who do not.[130,131] This is linked to the fact that the doubling time of prostate cancer is estimated to be 100 times faster than BPH. PSA doubling time is closely related to PSA velocity.

Part 4

Methods of tissue diagnosis of prostate cancer

Needle biopsies

The current standard method for detection of prostate cancer is by transrectal ultrasound-guided core biopsies. Directed biopsies to either lesions detected on digital rectal examination or on ultrasound should be combined with systematic biopsies taken according to a standardized protocol.[132,133] The sextant protocol samples the apex, mid, and base region bilaterally.[134] Sextant biopsies aim at the center of each half of the prostate equidistant from the midline and the lateral edge, while the most common location of prostate cancer is in the dorsolateral region of the prostate.

Several modifications of the sextant protocol have been proposed. Recent studies have shown that protocols with 10 or more systematic biopsies have a cancer detection rate up to 35% superior to the traditional sextant protocol.[135–137] This increased yield relates to the addition of biopsies sampling the more lateral part of the peripheral zone, where a significant number of cancers are located.

Approximately 15 to 22% of prostate cancers arise in the transition zone, while sextant biopsies mainly sample the peripheral zone. Most studies have found few additional cancers by adding transition zone biopsies to the sextant protocol (1.8 to 4.3% of all cancers detected) and transition zone biopsies are usually not taken in the initial biopsy session.[138,139]

Transurethral resection of the prostate

When transurethral resection of the prostate (TURP) is done without clinical suspicion of cancer, prostate cancer is incidentally detected in approximately 8–10% of the specimens. Cancers detected at TURP are often transition zone tumors, but they may also be of peripheral zone origin, particularly when they are large.[140–142] It is recommended that the extent of tumor is reported as a percentage of the total specimen area. If the tumor occupies less than 5% of the specimen it is stage T1a, and otherwise stage T1b. However, in the uncommon situation of less than 5% of cancer with Gleason score 7 or higher, patients are treated as if they had stage T1b disease. Most men who undergo total prostatectomy for T1a cancer have no or minimal residual disease, but in a minority there is substantial tumor located in the periphery of the prostate.[143]

Fine needle aspiration cytology

Before the era of transrectal core biopsies, prostate cancer was traditionally diagnosed by fine needle aspiration (FNA). FNA is still used in some countries and has some advantages. The technique is cheap, quick, usually relatively painless, and has a low risk of complications. In early studies comparing FNA and limited core biopsy protocols, the sensitivity of FNA was usually found to be comparable with that of core biopsies.[144] However, the use of FNA for diagnosing prostate cancer has disadvantages.

- Potential sources of false positive diagnosis with FNA are inflammatory atypia, prostatic intra-epithelial neoplasia, and contamination of seminal vesicle epithelium.
- Gleason grading, which is essential for the clinician, is based on the histologic architecture of glands and cannot be applied on cytology.
- Core biopsies, unlike FNA, provide information about tumor extent and occasionally about extraprostatic extension and seminal vesicle invasion.
- Before treatment of localized prostate cancer, the diagnosis should, therefore, be confirmed by core biopsies.

Part 5

Diagnostic criteria for prostate cancer

Macroscopy

Most clinically palpable prostate cancers diagnosed on needle biopsy are predominantly located posteriorly and posterolaterally.[145,146] In a few cases, large transition zone tumors may extend into the peripheral zone and become palpable. Cancers detected on TURP are predominantly within the transition zone. Non-palpable cancers detected on needle biopsy are predominantly located peripherally, although 15–25% have tumor predominantly within the transition zone.[147] Large tumors may extend into the central zone, yet cancers uncommonly arise in this zone. Multifocal adenocarcinoma of the prostate is present in more than 85% of prostates.[145]

On section, grossly evident cancers are firm, solid, and range in color from white-gray to yellow-orange, the latter having increased cytoplasmic lipid; the tumors contrast with the adjacent benign parenchyma, which is typically tan and spongy[141,148–150] (Figure 4.4). Tumors usually extend microscopically beyond their macroscopic border. Gross hemorrhage and necrosis are rare. Subtle tumors may be grossly recognized by structural asymmetry; for example, peripheral zone tumors may deform the periurethral fibromuscular concentric band demarcating the periurethral and peripheral prostate centrally, and peripherally may expand or obscure the outer boundaries of the prostate. Anterior and apical tumors are difficult to grossly identify because of admixed stromal and nodular hyperplasia.[148–152]

In general, grossly recognizable tumors tend to be larger, of higher grade and stage, and are frequently palpable, compared with grossly inapparent tumors (usually < 5 mm) which are often non-palpable, small, low-grade and low-stage.[153] Some large tumors are diffusely infiltrative, and may not be evident grossly.[149,152] Causes of gross false positive diagnoses include confluent glandular atrophy, healed infarcts,
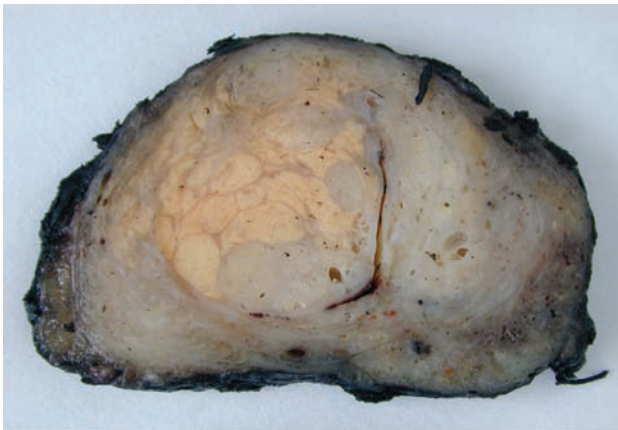
stromal hyperplasia, granulomatous prostatitis, and infection.[149] In countries with widespread PSA testing, grossly evident prostate cancer has become relatively uncommon.

Microscopy

The diagnosis of carcinoma relies on a combination of architectural and cytologic findings. The light microscopic features are usually sufficient, but cases with small suspicious foci may benefit from immunohistochemical studies (Table 4.4).

Architectural features

Architectural features are usually assessed at low- to medium-power magnification, with emphasis on spacing, size, and shape of acini. The arrangement of the acini is diagnostically useful and is the basis of the Gleason grade. Malignant acini usually have an irregular, haphazard arrangement, randomly scattered in the stroma in clusters or singly. The spacing between malignant acini often varies widely. Variation in acinar size is a useful criterion for cancer, particularly when small, irregular, abortive acini with primitive lumens are seen at the periphery of a focus of well-differentiated carcinoma.

The acini in suspicious foci are usually small or medium sized, with irregular contours that contrast with the typical smooth, round to elongated contours of benign and hyperplastic acini (Figure 4.5(A)). Comparison with the adjacent benign prostatic acini is always of value in the diagnosis of cancer. Well-differentiated carcinoma and the large acinar variant of Gleason grade 3 carcinoma are particularly difficult to separate from benign acini in needle biopsies because of the uniform size and spacing of acini; in such cases, greater emphasis is placed on cytologic features, immunohistochemical findings, and the presence of smaller diagnostic acini at the edge of the focus.

The basal cell layer is absent in prostate cancer, whereas an intact basal cell layer is present with benign acini. This is an important diagnostic feature that is not always easy to evaluate in routine tissue sections owing to false negative findings with atrophy and other mimics of cancer. Compressed stromal fibroblasts may mimic basal cells but are usually seen only focally at the periphery of acini. Small foci of adenocarcinoma sometimes cluster around or infiltrate near larger benign acini that have an intact basal cell layer, compounding the difficulty.

Figure 4.4
Macroscopic identification of areas of prostate cancer. Slice of the body of the prostate gland. Cancer is identified macroscopically in the transition zone.

Cytologic features

The cytologic features of adenocarcinoma include nuclear and nucleolar enlargement, which occurs in most malignant cells. Every

Table 4.4 Diagnostic criteria for carcinoma

Architectural features
■ Infiltrative pattern of malignant acini, e.g.:
  – arrangement: irregular and haphazard
  – spacing between acini varies widely
  – variation in size
  – irregular contour
■ Basal cell layer
  – absent

Cytologic features (secretory cells in single layer)
■ Nuclear hyperchromasia
■ Nuclear enlargement
■ Nucleolar enlargement or prominence
■ Mitotic figures
■ Amphophilic cytoplasm

Luminal findings
■ Crystalloids
■ Intraluminal blue mucin and/or pink amorphous secretions

Stromal findings
■ Collagenous micronodules

Immunohistochemical findings
■ Prostate-specific antigen
■ Prostatic acid phosphatase
■ 34βE12
■ p63
■ Racemase

Additional feature
■ Adjacent prostatic intra-epithelial neoplasia

cell has a nucleolus, so 'prominent' nucleoli (at least 1.50 μm in diameter or larger) are sought. Pathologists do not routinely measure nucleoli for diagnosis; this determination is based on comparison with benign epithelial cells elsewhere in the specimen (Figure 4.5(B)).

Artifacts often obscure the nuclei and nucleoli, and overstaining of nuclei by hematoxylin creates one of the most common and difficult problems in the interpretation of suspicious cells. Differences in fixation and handling of biopsy specimens influence nuclear size and chromasia, so comparison with cells from the same specimen is useful as an internal control. Many pathologists prefer pale staining with eosin, but this approach fails to accentuate nucleoli, which are often enlarged. In specimens with nuclear hyperchromasia and pale eosinophilic staining, we often increase the light source and magnification of suggestive foci to identify hidden enlarged nucleoli.

Luminal findings

Crystalloids are sharp, needle-like eosinophilic structures that are often present in the lumens of well-differentiated and moderately differentiated carcinoma[154] (Figure 4.5(A)). They are not specific for carcinoma and can be found in other conditions. The presence of crystalloids in metastatic adenocarcinoma of unknown site of origin is strong presumptive evidence of prostatic origin, although it is an uncommon finding and not conclusive.[155] Special stains highlight the presence of crystalloids that otherwise cannot be seen by light microscopy.[155] Crystalloids stain red with trichrome stain, blue with toluidine blue, and violet with the Mallory's staining. Crystalloids are argyrophilic with silver stain methods. No staining is observed with

periodic acid Schiff (PAS), Alcian blue, Prussian blue, and Congo red. Immunohistochemical stains for PSA and prostatic acid phosphatase (PAP) are negative. The pathogenesis of crystalloids is not known, but they probably result from abnormal protein and mineral metabolism within benign and malignant acini. Ultrastructurally, they are composed of electron-dense material that lacks the periodicity of crystals. Radiographic microanalysis reveals abundant sulfur, calcium, and phosphorus and a small amount of sodium.[154] Hard, proteinaceous secretions are almost always present in adjacent acini and are probably the source of the crystalloids.

Luminal acidic sulfated and non-sulfated mucin is often seen in acini of adenocarcinoma, appearing as amorphous or delicate, thread-like, faintly basophilic secretions in routine sections. This mucin stains with Alcian blue and is best displayed at pH 2.5, whereas normal prostatic epithelium contains PAS-reactive mucin that is neutral. Acidic mucin is not specific for carcinoma; it may be found in prostatic intra-epithelial neoplasia (PIN), atypical adenomatous hyperplasia, sclerosing adenosis, and, rarely, nodular hyperplasia.[156]

Occasionally, PCa may show the presence of intraluminal corpora amylacea. These are usually seen in normal ducts and acini, adenosis, and verumontanum mucosal gland hyperplasia.

Stromal findings

The stroma in cancer frequently contains young collagen, which appears lightly eosinophilic, although desmoplasia may be prominent. Muscle fibers in the stroma are sometimes split or distorted. However, this is a difficult feature to appreciate and cannot be relied upon because of the resemblance of the stroma associated with benign acini.

Collagenous micronodules (or mucinous fibroplasia) are a specific but infrequent and incidental finding in prostatic adenocarcinoma. They consist of microscopic nodular masses of paucicellular eosinophilic fibrillar stroma that impinge on acinar lumens[157] (Figure 4.5(C)). They are usually present in mucin-producing adenocarcinoma and result from extravasation of acidic mucin into the stroma. Collagenous micronodules are present in about 13% of cases of adenocarcinoma; they are not observed in benign epithelium, nodular hyperplasia, or PIN. They are an infrequent finding, present in 0.6% of needle biopsies and 12.7% of prostatectomies. Collagenous micronodules may be particularly valuable in challenging needle biopsy specimens.[157]

Immunohistochemical findings

The most important immunohistochemical markers in prostate pathology are prostate-specific antigen (PSA), PAP, high-molecular-weight keratin (34ßE12), p63, and AMACR. Promising new markers include prostate-specific membrane antigen and human glandular kallikrein 2 (hK2).[158] A useful confirmatory immunohistochemical stain to demonstrate urothelial origin is the combination of cytokeratin 7, cytokeratin 20, and thrombomodulin.

Immunohistochemical expression of PSA is useful for distinguishing high-grade prostate cancer from urothelial carcinoma, colonic carcinoma, granulomatous prostatitis, and lymphoma.[159] PSA also facilitates identification of the site of tumor origin in metastatic adenocarcinoma. PSA can be detected in frozen sections, paraffin-embedded sections, cell smears, and cytologic preparations of normal
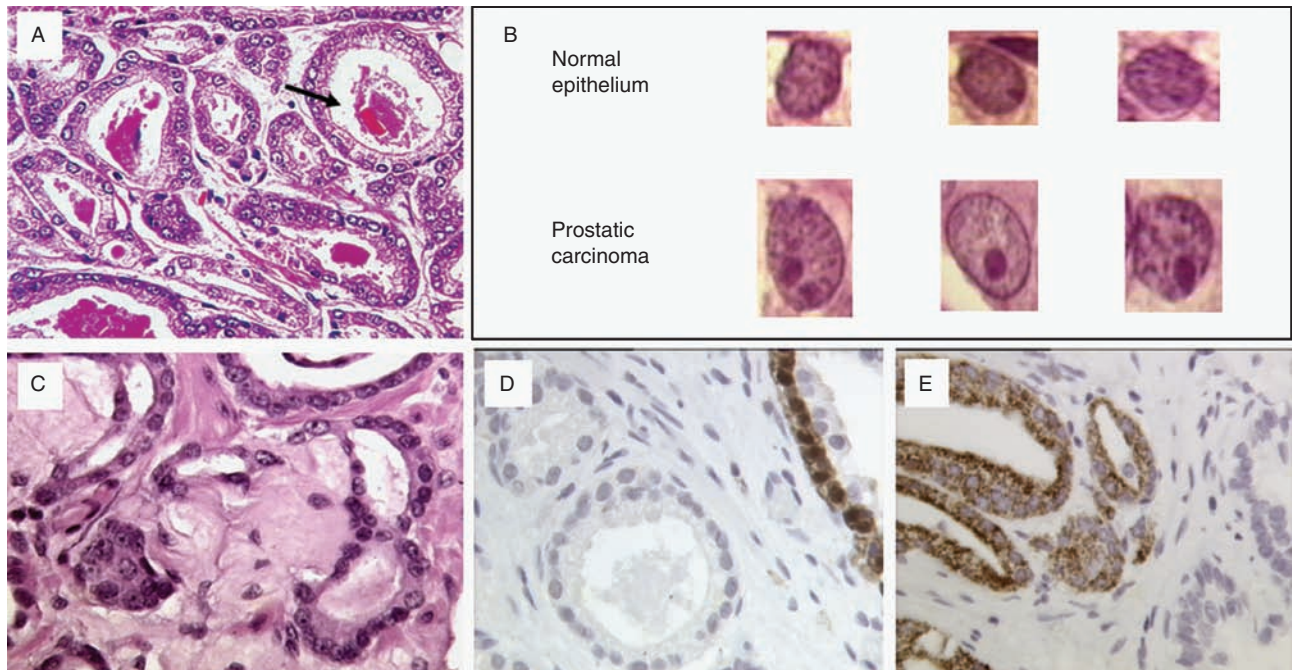
Figure 4.5
Microscopic features of adenocarcinoma. (A) The acini are usually small or medium sized, with irregular contours that contrast with the typical smooth, round to elongated contours of benign and hyperplastic acini. Crystalloids are present (arrow). (B) The cytologic features of adenocarcinoma include nuclear and nucleolar enlargement, which occurs in most malignant cells. This determination is based on comparison with benign epithelial cells elsewhere in the specimen. (C) Collagenous micronodules (or mucinous fibroplasia), i.e., microscopic nodular masses of paucicellular eosinophilic fibrillar stroma that impinge on acinar lumens. (D) Absence of a basal cell layer in prostatic adenocarcinoma (antibody against p63) (positive internal control: basal cells are present in the normal gland). (E) Adenocarcinoma labeled by an antibody directed against AMACR (P504S).

and neoplastic prostatic epithelium. Staining is invariably heterogeneous. Microwave antigen retrieval is usually not necessary, even in tissues that have been immersed in formalin for years. Formalin fixation is optimal for localization of PSA, and variation in staining intensity is only partially the result of fixation and embedding effects. Immunoreactivity is preserved in decalcified specimens and may be enhanced.

PAP is a valuable immunohistochemical marker for identifying prostate cancer when used in combination with PSA.[160] The intensity of PAP immunoreactivity correlates with patient survival, probably because immunoreactive cancer has greater androgen responsiveness.

In problem cases, using monoclonal antibodies directed against high-molecular-weight cytokeratin (for example, clone 34ßE12) may be useful for evaluation of the basal cell layer. We use this infrequently (in fewer than 5% of cases), however, and only as an adjunct to the light microscopic findings. The findings with this immunohistochemical stain should not be the basis for a diagnosis of malignancy, particularly in small suggestive foci. It is most useful in confirming the benignancy of a suggestive focus by showing an immunoreactive basal cell layer. Antikeratin 34ßE12 stains nearly all of the normal basal cells of the prostate; no staining occurs in the secretory and stromal cells.

Since uniform absence of a basal cell layer in prostatic acinar proliferations is one important diagnostic feature of invasive carcinoma and basal cells may be inapparent by hematoxylin and eosin (H&E) stain, basal cell specific immunostains may help to distinguish invasive prostatic adenocarcinoma from benign small acinar cancer mimics which retain their basal cell layer, e.g. glandular atrophy, post-atrophic hyperplasia, atypical adenomatous hyperplasia, sclerosing adenosis (atypical adenomatous hyperplasia), and radiation-induced atypia.[161–163] Because the basal cell layer may be interrupted or not demonstrable in small numbers of benign glands, the complete absence of a basal cell layer in a small focus of acini cannot be used alone as a definitive criterion for malignancy; rather, absence of a basal cell layer is supportive of invasive carcinoma only in acinar proliferations which exhibit suspicious cytologic and/or architectural features on H&E stain.[162] Conversely, some early invasive prostatic carcinomas, e.g. microinvasive carcinomas arising in association with or independent of high-grade PIN, may have residual basal cells.[164] Intraductal spread of invasive carcinoma and entrapped benign glands are other proposed explanations for residual basal cells.[161,163] Rare prostatic adenocarcinomas contain sparse neoplastic glandular cells which are immunoreactive for 34ßE12, yet these are not in a basal cell distribution.[102,161] The use of antibodies for 34ßE12 is especially helpful for the diagnosis of deceptively benign appearing variants of prostate cancer. Immunohistochemistry for cytokeratins 7 and 20 has a limited diagnostic use in prostate pathology with the exception that negative staining for both markers, which can occur in prostate adenocarcinoma, would be unusual for transitional cell carcinoma.[165]

p63, a nuclear protein encoded by a gene on chromosome 3q27–29 with homology to p53 (a tumor suppressor gene), has been shown to regulate growth and development in epithelium of the skin, cervix, breast, and urogenital tract. Specific isotypes are expressed in basal cells of stratified and pseudostratified epithelia (prostate,

bronchial), reserve cells of simple columnar epithelia (endocervical, pancreatic ductal), myoepithelial cells (breast, salivary glands, cutaneous apocrine/eccrine glands), urothelium, and squamous epithelium.[166] A monoclonal antibody is active in paraffin-embedded tissue following antigen retrieval. p63 has similar applications to those of high-molecular-weight cytokeratins in the diagnosis of prostatic adenocarcinoma, but with the advantages that p63:

■ stains a subset of 34βE12 negative basal cells,
■ is less susceptible to the staining variability of 34βE12 (particularly in TURP specimens with cautery artifact), and
■ is easier to interpret because of its strong nuclear staining intensity and low background.

Interpretative limitations related to presence or absence of basal cells in small numbers of glands for 34βE12 apply to p63, requiring correlation with morphology[102] (Figure 4.5(D)). Prostatic adenocarcinomas have occasional p63 immunoreactive cells, most representing entrapped benign glands or intraductal spread of carcinoma with residual basal cells.[166]

AMACR (α-methylacylCoA racemase) mRNA was recently identified as being overexpressed in prostatic adenocarcinoma by cDNA library subtraction utilizing high throughput RNA microarray analysis.[167] This mRNA was found to encode a racemase protein, for which polyclonal and monoclonal antibodies have been produced which are active in formalin-fixed, paraffin-embedded tissue.[168–170] Immunohistochemical studies on biopsy material with an antibody directed against AMACR (P504S) demonstrate that over 80% of prostatic adenocarcinomas are labeled[171] (Figure 4.5(E)). Certain subtypes of prostate cancer, such as foamy gland carcinoma, atrophic carcinoma, pseudohyperplastic, and treated carcinoma, show lower AMACR expression. However, AMACR is not specific for prostate cancer and is present in nodular hyperplasia (12%), atrophic glands (36%), HGPIN (>90%),[170] and atypical adenomatous hyperplasia (17.5%).[172] AMACR may be used as a confirmatory stain for prostatic adenocarcinoma, in conjunction with H&E morphology and a basal cell specific marker.[170] AMACR is expressed in other non-prostatic neoplasms including urothelial and colon cancer.

An immunoperoxidase cocktail containing monoclonal antibodies to cytokeratin 34βE12 and p63 is an effective basal cell stain. A cocktail containing 34βE12, p63, and racemase is also used.
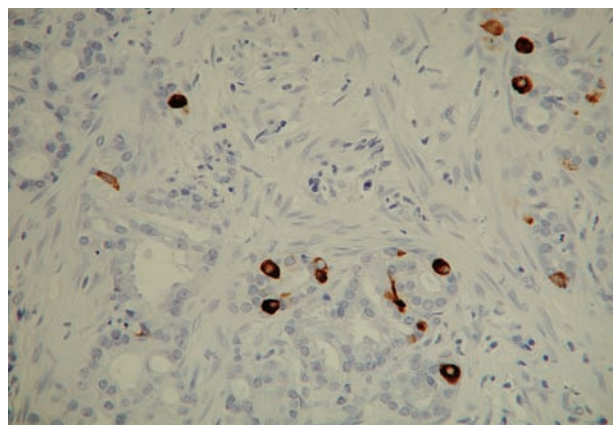
Figure 4.6
Prostatic adenocarcinoma with neuroendocrine cells detected by chromogranin A immunostaining.

Focal neuroendocrine differentiation

In 5–10% of prostatic carcinomas there are zones with a large number of single or clustered neuroendocrine cells detected by chromogranin A immunostaining[173–181] (Figure 4.6). A subset of these neuroendocrine cells may also be serotonin positive. Immunostaining for neuron-specific enolase, synaptophysin, bombesin/gastrin-releasing peptide, and a variety of other neuroendocrine peptides may also occur in individual neoplastic neuroendocrine cells, or in a more diffuse pattern,[182] and receptors for serotonin[183] and neuroendocrine peptides[184,185] may also be present. There are conflicting studies as to whether advanced androgen-deprived and androgen-independent carcinomas show increased neuroendocrine differentiation.[186–191] The prognostic significance of focal neuroendocrine differentiation in primary untreated prostatic carcinoma is controversial. In advanced prostate cancer, especially androgen-independent cancer, focal neuroendocrine differentiation portends a poor prognosis[186,188,189,191] and may be a therapeutic target.[192–194] (Additional information on the spectrum of neuroendocrine tumors is given in Parts 6 and 11).

Part 6

Histologic classification of carcinoma of the prostate

A wide variety of architectural patterns of adenocarcinoma may be seen in the prostate. Greater than 95% of all carcinomas of the prostate seen in needle biopsy specimens are referred to as acinar, microacinar, or conventional type (Figure 4.7(A)). Table 4.5 lists the histologic variants and subtypes of prostate cancer. Some of them are variants of acinar adenocarcinoma. Some of the rare variants and subtypes are described in separate subchapters (See also Part 11)

Pseudohyperplastic adenocarcinoma

Pseudohyperplastic prostate cancer resembles benign prostate glands in that the neoplastic glands are large with branching and papillary infolding.[195,196] The recognition of cancer with this pattern is based on the architectural pattern of numerous closely packed glands as well as nuclear features more typical of carcinoma. One pat- tern of pseudohyperplastic adenocarcinoma consists of numerous large glands that are almost back-to-back with straight, even, luminal borders, and abundant cytoplasm. Comparably sized benign glands either have papillary infoldings or are atrophic. The presence of cytologic atypia in some of these glands further distinguishes them from benign glands. It is almost always helpful to verify pseudohy- perplastic cancer with the use of immunohistochemistry to verify the absence of basal cells.

Pseudohyperplastic cancer, despite its benign appearance, may be associated with typical intermediate grade cancer and can exhibit aggressive behavior (i.e., extraprostatic extension).

Foamy gland adenocarcinoma

Foamy gland cancer is a variant of acinar adenocarcinoma of the prostate that is characterized by having abundant foamy appearing cytoplasm with a very low nuclear to cytoplasmic ratio. Although
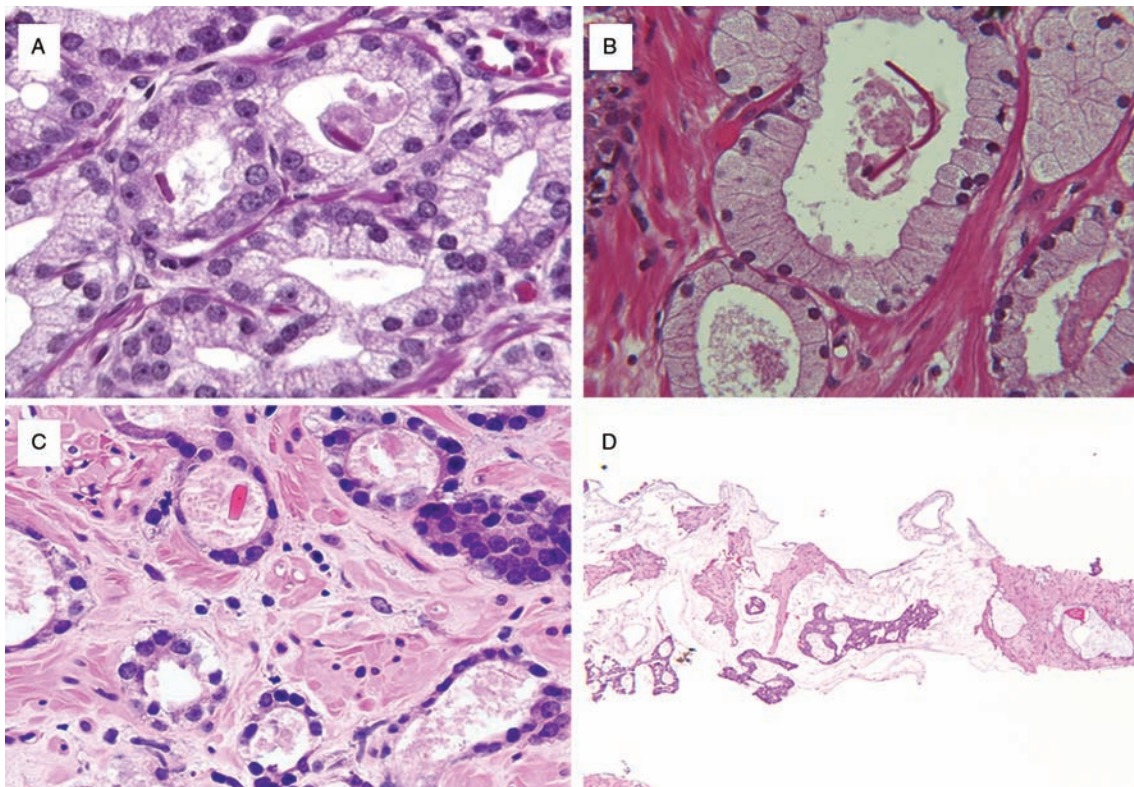
Figure 4.7
(A) Adenocarcinoma of acinar or conventional type. (B) Foamy gland adenocarcinoma. (C) Atrophic adenocarcinoma. (D) Mucinous adenocarcinoma.

Table 4.5 Histologic classification of carcinoma of the prostate

1. Adenocarcinoma (acinar, conventional, not otherwise specified)
2. Variants of adenocarcinoma and other carcinomas
   - Pseudohyperplastic adenocarcinoma
   - Foamy gland adenocarcinoma
   - Atrophic adenocarcinoma
   - Adenocarcinoma with glomeruloid features
   - Mucinous (colloid) adenocarcinoma
   - Signet-ring cell carcinoma
   - Oncocytic adenocarcinoma
   - Lymphoepithelioma-like carcinoma
   - Undifferentiated carcinoma, not otherwise specified
   - Prostatic duct adenocarcinoma
   - Small cell carcinoma and other neuroendocrine tumors
   - Sarcomatoid carcinoma
   - Basal cell carcinoma
   - Urothelial carcinoma
   - Adenosquamous carcinoma
   - Squamous cell carcinoma

the cytoplasm has a xanthomatous appearance (Figure 4.7(B)), it does not contain lipid, but rather empty vacuoles.[197] More typical cytologic features of adenocarcinoma such as nuclear enlargement and prominent nucleoli are frequently absent, which makes this lesion difficult to recognize as carcinoma, especially on biopsy material. Characteristically, the nuclei in foamy gland carcinoma are small and densely hyperchromatic. Nuclei in foamy gland cancer are round, more so than those of benign prostatic secretory cells. In addition to the unique nature of its cytoplasm, it is recognized as carcinoma by its architectural pattern of crowded and/or infiltrative glands, and frequently present dense pink acellular secretions.[198] In most cases, foamy gland cancer is seen in association with ordinary adenocarcinoma of the prostate.

In almost all such cases, despite foamy gland cancer's benign cytology, the ordinary adenocarcinoma component is not low grade. Consequently, foamy gland carcinoma appears best classified as intermediate grade carcinoma.

Atrophic adenocarcinoma

Most prostate cancers have abundant cytoplasm. An unusual variant of prostate cancer resembles benign atrophy owing to its scant cytoplasm. Although ordinary prostate cancers may develop atrophic cytoplasm as a result of treatment (see also Part 8), atrophic prostate cancers are usually unassociated with such a prior history.[199,200]

The diagnosis of carcinoma in these cases may be based on several features. First, atrophic prostate cancer may demonstrate a truly infiltrative process with individual small atrophic glands situated between larger benign glands. In contrast, benign atrophy has a lobular configuration. A characteristic finding in some benign cases of atrophy is the presence of a centrally dilated atrophic gland surrounded by clustered smaller glands, which has been termed 'post-atrophic hyperplasia'.[201] Although the glands of benign atrophy may appear infiltrative on needle biopsy, they are not truly infiltrative, as individual benign atrophic glands are not seen infiltrating in between larger benign glands. Whereas some forms of atrophy are

associated with fibrosis, atrophic prostate cancer lacks such a desmoplastic stromal response. Atrophic prostate cancer may also be differentiated from benign atrophy by the presence of marked cytologic atypia. Atrophy may show enlarged nuclei and prominent nucleoli, although not the huge eosinophilic nucleoli seen in some atrophic prostate cancers. Finally, the concomitant presence of ordinary less atrophic carcinoma can help in recognizing the malignant nature of the adjacent atrophic cancer glands (Figure 4.7(C)).

Adenocarcinoma with glomeruloid features

Prostatic adenocarcinoma with glomeruloid features is characterized by intraluminal ball-like clusters of cancer cells reminiscent of renal glomeruli, which we refer to as prostatic adenocarcinoma with glomeruloid features. Glomeruloid structures in the prostate represent an uncommon but distinctive pattern of growth that is specific for malignancy. Glomeruloid features may be a useful diagnostic clue for malignancy, particularly in some challenging needle biopsy specimens. This pattern of growth is usually seen in high-grade adenocarcinoma, often with extraprostatic extension. Glomeruloid features were not observed in any benign or premalignant lesions, including hyperplasia and intra-epithelial neoplasia.[202]

Mucinous and signet-ring cell adenocarcinoma

The diagnosis of mucinous adenocarcinoma of the prostate gland should be made when at least 25% of the tumor resected contains lakes of extracellular mucin (Figure 4.7(D)). Mucinous (colloid) adenocarcinoma of the prostate gland is one of the least common morphologic variants of prostatic carcinoma.[203–205] In contrast to bladder adenocarcinomas, mucinous adenocarcinomas of the prostate rarely contain mucin-positive signet cells.

Mucinous prostate adenocarcinomas behave aggressively.[203–205] In the largest reported series, 7 of 12 patients died of tumor (mean 5 years) and 5 were alive with disease (mean 3 years). Although these tumors are not as hormonally responsive as their non-mucinous counterparts, some respond to androgen withdrawal. Mucinous prostate adenocarcinomas have a propensity to develop bone metastases and increased serum PSA levels with advanced disease.

Some carcinomas of the prostate will have a signet-ring cell appearance, yet the vacuoles do not contain intracytoplasmic mucin.[206] These vacuolated cells may be present as singly invasive cells, in single glands, and in sheets of cells. Only a few cases of prostate cancer have been reported with mucin-positive signet cells.[207,208]

One should exclude other mucinous tumors of non-prostatic origin based on morphology and immunohistochemistry and, if necessary, using clinical information.

Oncocytic adenocarcinoma

Prostatic adenocarcinomas are composed of large cells with granular eosinophilic cytoplasm. Tumor cells have round to ovoid hyperchromatic nuclei and are strongly positive for PSA. Numerous

mitochondria are seen on ultrastructural examination. A high Gleason grade,[209,210] elevated serum PSA,[210] and metastasis of similar morphology[209] have been reported.

Lymphoepithelioma-like carcinoma

This undifferentiated carcinoma is characterized by a syncytial pattern of malignant cells associated with a heavy lymphocytic infiltrate. Malignant cells are PSA-positive. Associated acinar adenocarcinoma has been noted.[211,212] In situ hybridization has been negative for Epstein–Barr virus.[211] Clinical significance is uncertain.

Prostatic ductal adenocarcinoma

Subtype of adenocarcinoma composed of larger glands lined by tall pseudostratified columnar cells. *Endometrial carcinoma* was originally used to describe this entity because of its morphologic similarity to endometrium. In pure form, ductal adenocarcinoma accounts for 0.2 to 0.8% of prostate cancers.[213–215] More commonly it is seen with an acinar component.

Ductal adenocarcinoma may be located centrally around the prostatic urethra (Figure 4.8) or more frequently located peripherally admixed with typical acinar adenocarcinoma. A centrally located adenocarcinoma may also be associated with a peripherally located acinar adenocarcinoma. Centrally occurring tumors appear as exophytic polypoid or papillary masses protruding into the urethra around the verumontanum. Peripherally occurring tumors typically show a white-gray firm appearance similar to acinar adenocarcinoma.

Periurethral or centrally located ductal adenocarcinoma may cause hematuria, urinary urgency, and eventually urinary retention. In these cases, there may be no abnormalities on rectal examination. Tumors arising peripherally may lead to enlargement or induration of the prostate.
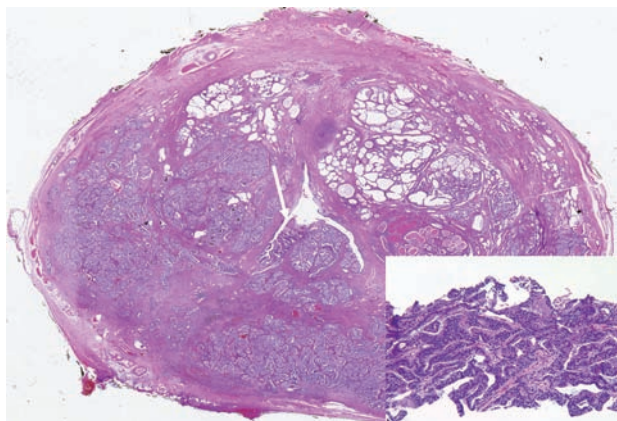
Figure 4.8
Ductal adenocarcinoma located centrally around the prostatic urethra and involving the verumontanum, associated with a peripherally located adenocarcinoma. (Insert: preoperative biopsy: ductal adenocarcinoma with papillary pattern.)

Serum PSA levels may be normal, particularly in a patient with only centrally located tumor. In most cases, transurethral resections performed for diagnosis or relief of the urinary obstruction will provide sufficient diagnostic tissue. Transrectal needle core biopsies may also obtain diagnostic tissue when the tumor is more peripherally located.[216] In addition, areas of ductal adenocarcinoma may be incidentally identified in prostatectomy specimens.

Microscopy

Ductal adenocarcinoma is characterized by tall columnar cells with abundant usually amphophilic cytoplasm, which form a single (Figure 4.8) or pseudostratified layer reminiscent of endometrial carcinoma. The cytoplasm of ductal adenocarcinoma is often amphophilic and may occasionally appear clear. In some cases, there are numerous mitoses and marked cytologic atypia. In other cases, the cytologic atypia is minimal, which makes a diagnosis difficult, particularly on needle biopsy. Peripherally located tumors are often admixed with cribriform, glandular, or solid patterns, as seen in acinar adenocarcinoma.

Although ductal adenocarcinomas are not typically graded, they are mostly equivalent to Gleason pattern 4. In some cases comedo necrosis is present whereby they could be considered equivalent to Gleason pattern 5. Ductal adenocarcinoma displays a variety of architectural patterns which are often intermingled:[217,218] papillary, cribriform, individual gland, and solid (Figure 4.8, insert: preoperative biopsy).

Immunohistochemically ductal adenocarcinoma is strongly positive for PSA and PAP. Tumor cells are typically negative for basal cell specific high-molecular-weight cytokeratin (detected by 34βE12); however, pre-existing ducts may be positive for this marker.

Ductal adenocarcinoma usually spreads along the urethra or into the prostatic ducts with or without stromal invasion. Other patterns of spread are similar to that of acinar prostatic adenocarcinoma with invasion to extraprostatic tissues and metastasis to pelvic lymph nodes or distal organs. Ductal adenocarcinomas appear to have a tendency to metastasize to lung and penis.

Differential diagnosis

Ductal adenocarcinoma must be distinguished from urothelial carcinoma, ectopic prostatic tissue, benign prostatic polyps, and proliferative papillary urethritis. One of the more difficult differential diagnoses is cribriform high-grade prostatic intra-epithelial neoplasia. Some patterns of ductal adenocarcinoma may represent *ductal carcinoma in situ*.

Prognosis

Most studies have demonstrated that ductal adenocarcinoma is aggressive. Some reported that 25–40% of cases had metastases at the time of diagnosis with a poor 5-year survival rate ranging from 15 to 43%.[214,219,220] Limited ductal adenocarcinoma on biopsy warrants definitive therapy. Androgen deprivation therapy may provide palliative relief, even though these cancers are less hormonally responsive than acinar adenocarcinoma.

Small cell carcinoma

Small cell carcinomas of the prostate histologically are identical to small cell carcinomas of the lung[221,222] (Figure 4.9). In approximately 50% of the cases, the tumors are mixed small cell carcinoma and adenocarcinoma of the prostate. Neurosecretory granules have been demonstrated within several prostatic small cell carcinomas. Using immunohistochemical techniques small cell components are negative for PSA and PAP. There are conflicting studies as to whether small cell carcinomas of the prostate are positive for thyroid transcription factor-1 (TTF-1), in order to distinguish them from a metastasis from the lung.[223,224]
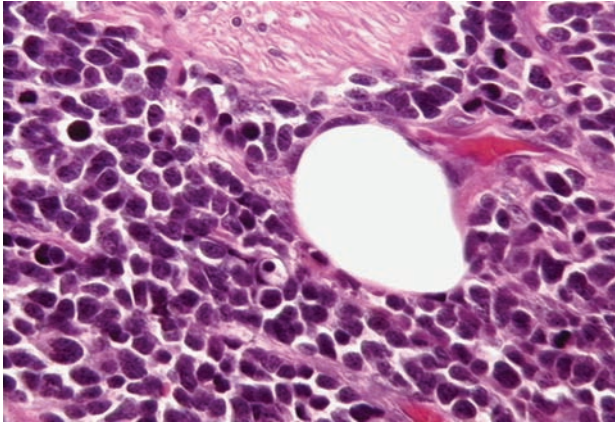
Figure 4.9
Small cell carcinoma.

Prognosis

The average survival of patients with small cell carcinoma of the prostate is less than a year. There is no difference in prognosis between patients with pure small cell carcinomas and those with mixed glandular and small cell carcinomas. The appearance of a small cell component within the course of adenocarcinoma of the prostate usually indicates an aggressive terminal phase of the disease.

Sarcomatoid (carcinosarcoma) carcinoma

There is considerable controversy in the literature regarding nomenclature and histogenesis of these tumors. In some series, carcinosarcoma and sarcomatoid carcinoma are considered as separate entities based on the presence of specific mesenchymal elements in the former. However, given their otherwise similar clinicopathologic features and identically poor prognosis, these two lesions are best considered as one entity. Sarcomatoid carcinoma of the prostate is a rare neoplasm composed of both malignant epithelial and malignant spindle-cell and/or mesenchymal elements.[225–230] Sarcomatoid carcinoma may be present in the initial pathologic material (synchronous presentation) or there may be a previous history of adenocarcinoma treated by radiation and/or hormonal therapy.[231]

The gross appearance often resembles sarcomas. Microscopically, sarcomatoid carcinoma is composed of a glandular component
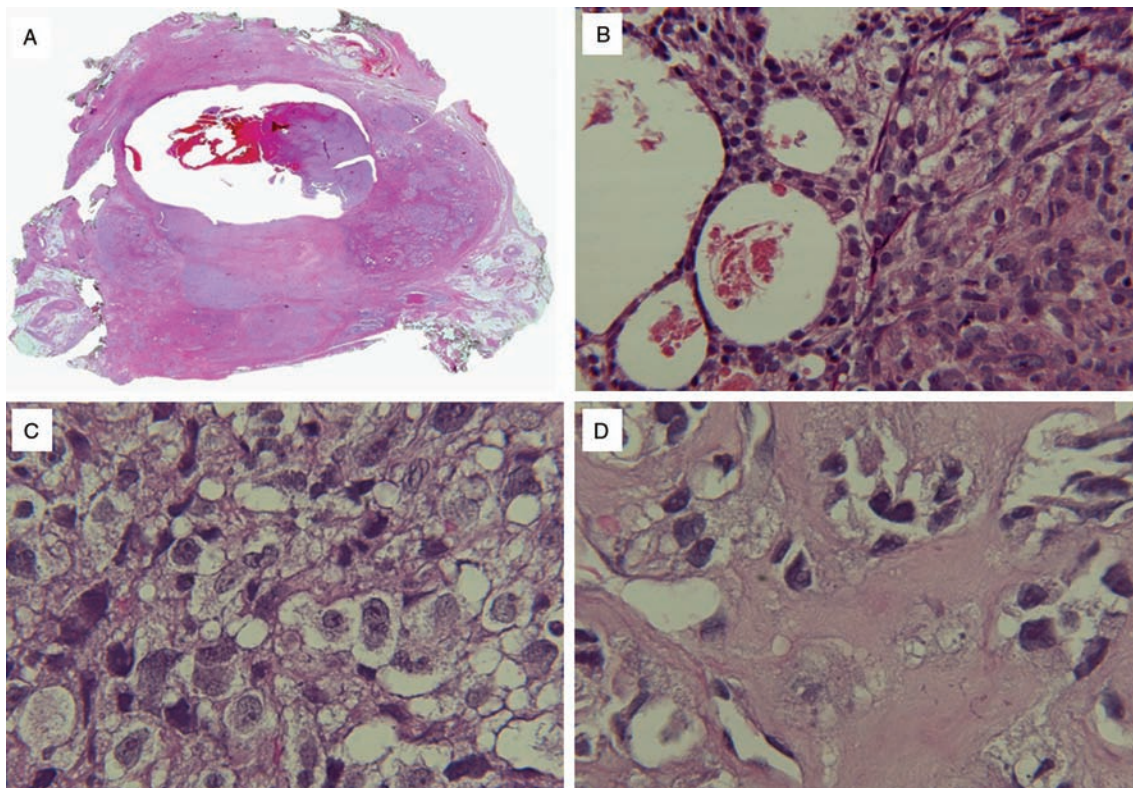
Figure 4.10
(A) Sarcomatoid (carcinosarcoma) carcinoma extending into the urethra. (B) Glandular component with adjacent solid area. (C) Undifferentiated tumor area. (D) Osteosarcoma pattern.

showing variable Gleason score[227,232] (Figures 4.10(A)–(C)). The sarcomatoid component often consists of a non-specific malignant spindle-cell proliferation. Amongst the specific mesenchymal elements are osteosarcoma (Figure 4.10(D)), chondrosarcoma, rhabdomyosarcoma, leiomyosarcoma, liposarcoma, angiosarcoma, or multiple types of heterologous differentiation.[227,231] Sarcomatoid carcinoma should be distinguished from the rare carcinoma with metaplastic, benign-appearing bone or cartilage in the stroma.

By immunohistochemistry, epithelial elements react with antibodies against PSA and/or pan-cytokeratins, whereas spindle-cell elements react with markers of soft tissue tumors and variably express cytokeratins.

Prognosis

Serum PSA is within normal limits in most cases. Nodal and distant organ metastases at diagnosis are common.[227,231,232] There is less than a 40% 5-year survival.[227]

Part 7

Current clinical practice of Gleason grading of prostate cancer

The Gleason grading system for prostate cancer, named after Donald F Gleason, is the predominant grading system around the world.[233–235] The Gleason grading system is based on glandular architecture which can be divided into five patterns of growth (also known as grades) with decreasing differentiation.[233–236] The primary and secondary pattern or grade, i.e. the most prevalent and the second most prevalent pattern or grade, are added to obtain a Gleason score or sum that is to be reported.[233,236] Nuclear atypia or cytoplasmic features are not evaluated. An important issue is that the initial grading of prostate carcinoma should be performed at low magnification.[237,238] Then one may proceed with high-power objectives to look for rare fused glands or a few individual cells. Gleason grading of prostate cancer has changed over the years to adapt to needle biopsies and radical prostatectomy specimens that were unavailable at the time when Gleason proposed his system.[1,61,62,238–245]

Gleason grading remains one of the most significant factors in the clinical decision-making activity, both in needle biopsy specimens and after radical prostatectomy is performed; i.e. it predicts pathologic stage, margin status, biochemical failure, local recurrences, lymph node, disease progression, or distant metastasis after prostatectomy.[61,151,246–251] Radiation therapy, radical prostatectomy, and other therapies are initially based on the Gleason score; in practice, Gleason scores of 7–10 are associated with worse prognosis while Gleason scores of 5–6 are associated with lower progression rates after therapy.[62,252,253] In recent years, Gleason score has been included in clinical nomograms which are used with increasing frequency to predict disease progression.[1,254–262]

Gleason patterns (Figure 4.11)

- Gleason pattern 1: very well-circumscribed nodule of separate, closely packed glands which do not infiltrate into adjacent benign prostatic tissue. The glands are of intermediate size and approximately equal in size and shape. The nucleus is typically small and cytoplasm frequently is abundant and pale-staining. Nuclear and cytoplasm appearance are not taken into account in diagnosis. This pattern is exceedingly rare and usually seen in transition zone cancers (Tables 4.6 and 4.7).
- Gleason pattern 2: round to oval glands with smooth ends. The glands are more loosely arranged and not quite as uniform in size and shape as those of Gleason pattern 1. There may be minimal invasion by neoplastic glands into the surrounding non-neoplastic prostatic tissue. The glands are of intermediate size and larger than in Gleason pattern 1. The variation in glandular size and separation between glands is less than that seen in pattern 3. Although not evaluated in Gleason grading, the cytoplasm of Gleason pattern 2 cancers is abundant and pale-staining. Gleason pattern 2 is usually seen in transition zone cancers but may occasionally be found in the peripheral zone.

- Gleason pattern 3: is the most common pattern but is morphologically heterogeneous. The glands are infiltrative and the distance between them is more variable than in patterns 1 and 2. Malignant glands often infiltrate between adjacent non-neoplastic glands. The glands of pattern 3 vary in size and shape and are often angular. Small glands are typical for pattern 3, but there may also be large and irregular glands. Each gland has an open lumen and is circumscribed by stroma. Cribriform pattern 3 is rare and difficult to distinguish morphologically from cribriform HGPIN. The latter shows the presence of basal cells. These are lacking in cribriform pattern 3 prostate cancer. This heterogeneous expression of Gleason grade 3 raised an initial subdivision into patterns A, B, and C, respectively.
- Gleason pattern 4: glands appear fused, cribriform, or they may be poorly defined and small. Fused glands are composed of a group of glands that are no longer completely separated by stroma. The edge of a group of fused glands is scalloped and there are occasional thin strands of connective tissue within this group. The hypernephroid pattern described by Gleason is a rare variant of fused glands with clear or very pale-staining cytoplasm. Cribriform pattern 4 glands are large or they may be irregular with jagged edges. As opposed to fused glands, there are no strands of stroma within a cribriform gland. Most cribriform invasive cancers should be assigned a pattern 4 rather than pattern 3. Poorly defined glands do not have a lumen that is completely encircled by epithelium.
- Gleason pattern 5: almost complete loss of glandular lumina which are only occasionally present. The epithelium forms solid sheets, solid strands, or single cells invading the stroma; comedo necrosis may be present. Care must be applied when assigning a Gleason pattern 4 or 5 to limited cancer on needle biopsy to exclude an artifact of tangential sectioning of lower grade cancer.

Reporting Gleason scores in prostate needle biopsies

Gleason score 2–4

The diagnosis of Gleason score 2–4 on needle biopsies should be made 'rarely, if ever', and the reasons are compelling:[238] (1) Gleason score 2–4 cancer is extraordinarily rare in needle biopsies as compared to transurethral resection specimens; (2) there is poor reproducibility among experts;[237,263,264] (3) the correlation with the prostatectomy score is poor; and (4) a 'low' score of Gleason 2–4 may misguide clinicians into believing that there is an indolent tumor.[253] A recent consensus stated that a Gleason score of 1 + 1 = 2 is a grade that should not be diagnosed regardless of the type of specimen with extremely rare exception, since most of these cases in the era of Gleason, would
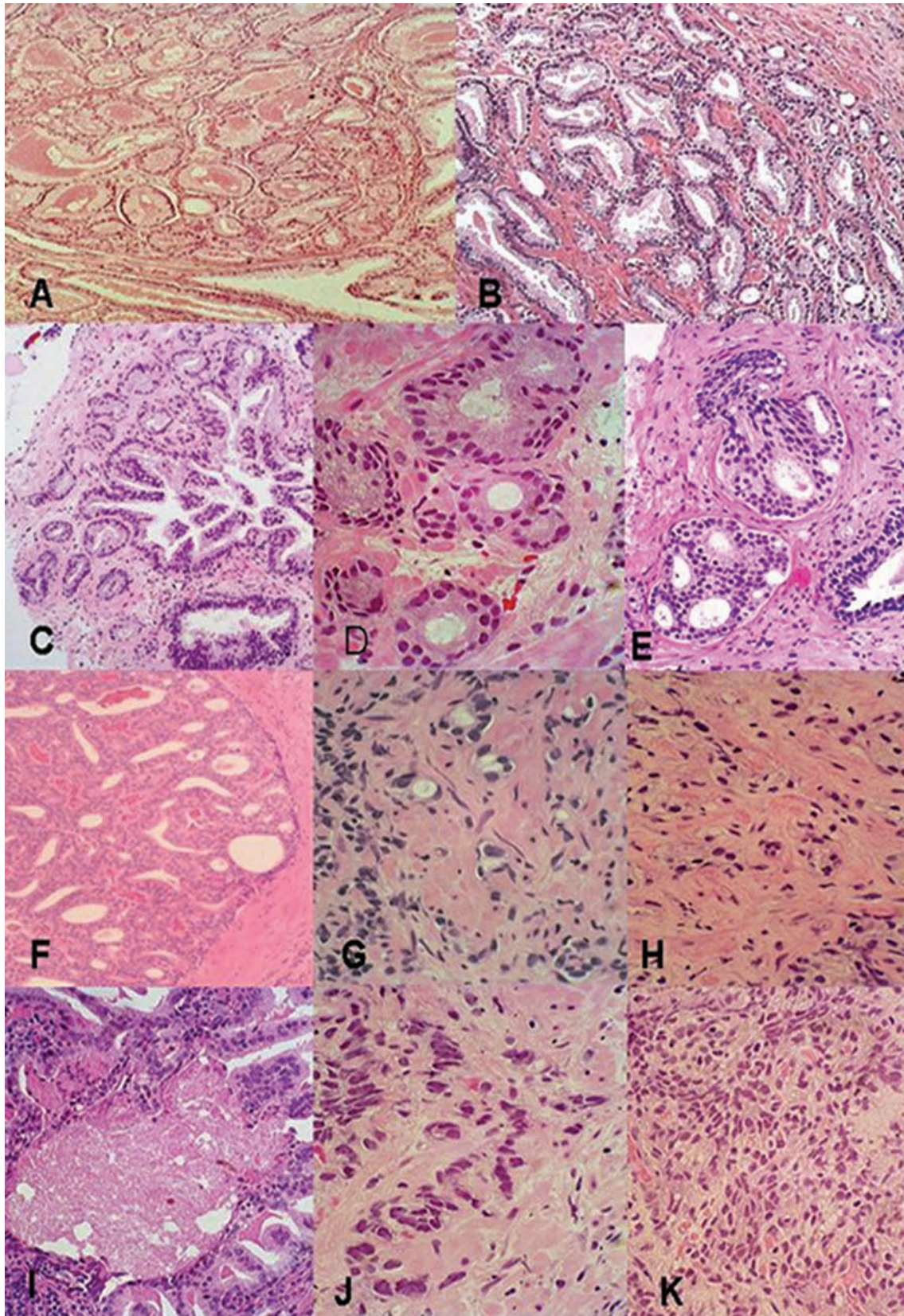
Figure 4.11
Examples of Gleason patterns 1 (A), 2 (B), 3 (C, D, E), 4 (F, G, H), and 5 (I, J, K). Reproduced with permission from Lopez-Beltran et al. Current practice of Gleason grading of prostate carcinoma. Virch Arch 2006; 448: 111–18.

Table 4.6 Gleason grades (patterns)

- Grade 1: single, separate, closely packed acini
- Grade 2: single acini, more loosely arranged, less uniform
- Grade 3: single acini of variable size, and separation, cribriform and papillary patterns
- Grade 4: irregular masses of acini and fused epithelium, can show clear cells
- Grade 5: anaplastic carcinoma

Table 4.7 Diagnostic reporting of Gleason score

General features
- Perform Gleason grading at low magnification using a 4 × or 10 × lens
- Report primary pattern and secondary pattern and assign Gleason score
- If only one pattern is present, double it to yield Gleason score. A Gleason score is usually assignable even if the cancer is extremely small
- In a needle biopsy with more than 2 patterns (tertiary pattern), the worst pattern must be reflected in the Gleason score even if it is not the predominant or secondary pattern, use the rule 'the most and the worst' (see text)
- In a radical prostatectomy with more than 2 patterns, the primary and secondary patterns must be reflected in the Gleason score. Add tertiary pattern as a note in the report
- Provide Gleason score for each separately involved core when identified and give overall Gleason score when mixed in one container
- In general a diagnosis of Gleason score 2–4 should not be made
- Do not report Gleason score after hormonal or radiation therapy except if cancer shows no treatment effect

Optional features
- Provide percent of tumor with Gleason pattern 4 in Gleason score 7
- Provide percent of tumor with Gleason patterns 4 and 5 in tumors with Gleason score 8–10

today be referred to as adenosis (atypical adenomatous hyperplasia) because of improvement in recognizing basal cells.[238,252,265] Cribriform morphology is not allowed within Gleason pattern 2.[246]

Gleason pattern 3

Cribriform pattern 3 applies to round, well-circumscribed glands of the same size of normal glands, but only rare cribriform lesions satisfy these criteria. Therefore the majority of cribriform patterns should be diagnosed as Gleason pattern 4. 'Individual cells' would not be allowed within Gleason pattern 3.[238,241,246]

Gleason pattern 4 in Gleason score 7 tumors

The importance of the percentage of Gleason 4 pattern in Gleason score 7 tumors accumulates rapidly.[238,241,244,258,262,266,267] In recently

generated nomograms, patients with Gleason score 4 + 3 vs 3 + 4 are stratified differently.[257] Whether or not the percentage of pattern 4 tumor should be included in the report remains optional at the present time. Small, ill-defined glands with poorly formed glandular lumina also warrant the diagnosis of Gleason pattern 4 as stated by a recent consensus.[238]

Gleason pattern 5

Comedo necrosis, when seen in solid nests or cribriform masses, should be regarded as Gleason pattern 5. However, the definition of comedo necrosis requires intraluminal necrotic cells and/or nuclear debris (karyorrhexis).[238]

Tertiary pattern

Another important change recently incorporated in current practice is the recognition and reporting of the tertiary pattern in needle biopsies.[266,268] This includes tumors with patterns 3, 4, and 5 in various proportions on a biopsy. Tertiary patterns are uncommon but when the worst Gleason grade is the tertiary pattern, it should influence the final Gleason score, and therefore the primary pattern and the highest grade should be recorded following the rule of 'the most and the worst'.[238] For example: a case with primary Gleason pattern 3, secondary pattern 4, and tertiary pattern 5 should be assigned a Gleason score of 8. These tumors should be classified overall as high-grade (Gleason score 8–10).[261,268]

Needle biopsy with different cores showing different grades

This is related to when one or more of the cores shows pure high-grade cancer (i.e. Gleason score 4 + 4 = 8) and the other cores show pattern 3 (3 + 3, 3 + 4, or 4 + 3) cancer.[238,244,256,269] If one reports the grades of each core separately, the highest-grade tumor (Gleason score 8) would typically be the one selected by the clinician as the grade of the entire case. Others give instead an overall score for the entire case. For example, in a case with Gleason score 4 + 4 = 8 on one core with pattern 3 (3 + 3 = 6, 3 + 4 = 7, 4 + 3 = 7) on other cores, the overall score for the entire case would be Gleason score 4 + 3 = 7 or 3 + 4 = 7, depending on whether pattern 4 or 3 predominated. Likewise, it was demonstrated that when one core is Gleason score 4 + 4 = 8 with other cores having pattern 3, the pathologic stage at radical prostatectomy is comparable to cases with all needle cores having Gleason score 4 + 4 = 8.[61,238,241,247–249] The use of the highest core grade of the given case in cases where there are multiple cores of different grades advocated in current tables and nomograms gives additional support for giving cores a separate grade rather than an overall score for the entire case. This is the rationale of a recent survey in which 81% of urologists used the highest Gleason score on a positive biopsy, regardless of the overall percentage involvement, to determine treatment.[260] Consequently, is has been recommended to assign individual Gleason scores to separate cores as long as the cores are submitted in separate containers or the cores are in the same container yet specified by the urologist

as to their location (i.e. by different color inks). In addition, one has the option to also give an overall score at the end of the case.[244,270]

In cases where a container contains multiple pieces of tissue and one cannot be sure if one is looking at an intact core, it is recommended that one should only give an overall score for that container.[238]

Reporting Gleason scores in radical prostatectomies

In these specimens one should assign the Gleason score based on the primary and secondary patterns with a comment if present on the tertiary pattern.[61,238,241]

Gleason scores 2–4

Gleason scores 2–4 are rarely seen as the grade of the main tumor in radical prostatectomies performed for stages T1c or T2 disease. These tumors are typically seen in multifocal incidental adenocarcinoma of the prostate found within the transition zone in transurethral resection (TURP) specimens.[238,241,252] The situation where Gleason scores 2–4 tumor represents the major tumor at radical prostatectomy performed for tumor incidentally found on TURP (stages T1a and T1b) is uncommon. In one study Gleason score 2–4 was the grade of the main tumor in 2% of the radical prostatectomy specimens; this represents a disproportionate number of T1a and T1b tumors as compared to what would be currently seen in today's practice. All men with only Gleason scores 2–4 tumor at radical prostatectomy are cured.[238,241]

Gleason scores 5–6

It is important to recognize that the majority of tumors with Gleason scores 5–6 are cured after radical prostatectomy.[238,255]

Gleason score 7

Tumors with a Gleason score of 7 have a significantly worse prognosis than those with a Gleason score of 6. Given the adverse prognosis associated with Gleason pattern 4, one would expect that whether a tumor is Gleason score 3 + 4 versus 4 + 3 would influence prognosis.[255] There have been several studies addressing Gleason score 3 + 4 as compared to Gleason score 4 + 3 at radical prostatectomy with somewhat conflicting results. In one study they reported no significant survival advantage for Gleason pattern 3 + 4 over 4 + 3, but another study showed Gleason score 3 + 4 versus 4 + 3 correlated with both stage and progression in men with serum PSA values <10 ng/ml and organ-confined disease.[1,257,262] Several other investigations have shown that Gleason score 4 + 3 has a worse prognosis. This is an issue in which much work needs to be done.

Gleason scores 8–10

Gleason scores 8–10 may account for only 7% of the grades seen at radical prostatectomy, but these patients have highly aggressive tumors with advanced stage such that they are not amenable to surgical therapy alone. Overall, patients with Gleason scores 8–10 at radical prostatectomy have a 15% chance of having no evidence of disease at 15 years following surgery.[255,270]

Percent Gleason pattern 4/5

The proportion of high-grade tumor as the preferred method for grading prostate cancer has been proposed as it is predictive for progression at the extremes (greater than 70% or less than 20% pattern 4/5).[250,251] It has been recently demonstrated that classifying tumors based on the combined percent of pattern 4/5 is more predictive than stratifying patients into Gleason score alone. Therefore, it has been recommended that it should be included in the report.[251]

Tertiary Gleason pattern

In radical prostatectomy a higher proportion of cases is found to contain more than two grades and over 50% of them contain at least three different grades.[151,238] The progression rate of Gleason scores 5–6 tumors with a tertiary component of Gleason pattern 4 is almost the same as those of pure Gleason score 7 tumors. Gleason score 7 tumors with tertiary pattern 5 experience progression rates following radical prostatectomy approximating pure Gleason 8 tumors.[258,268] On the other hand, no such significance could be seen in cases of Gleason (4 + 4) score 8 with tertiary pattern 5; since Gleason score 8 tumors are already aggressive, the existence of pattern 5 elements adds no difference. These tumors should be graded routinely (primary and secondary patterns) with a comment in the report noting the presence of the tertiary element. In the setting of high grade cancer (score 8–10) one should ignore lower-grade patterns if they occupy less than 5% of the area of the tumor.[244,245]

Tumors with one predominant pattern and a small percentage of higher grade tumor

Some controversy still exists on how to grade tumors, which are over 95% of one pattern, where there is only a very small percentage of higher-grade tumor. For example, in the case of a tumor composed of >95% Gleason pattern 3 and <5% pattern 4, some experts would assign a Gleason score 3 + 3 = 6, as it has been proposed that one needs over 5% of a pattern to be present for it to be incorporated within the Gleason score. Others might grade the tumor as Gleason score 3 + 4 = 7. It seems that the existence of a high-grade component, even if it constitutes less than 5% of the whole tumor, has a significant adverse influence.[238,253]

Radical prostatectomy specimens with separate tumor nodules

It was recommended that radical prostatectomy specimens should be processed in an organized fashion where one can make some

assessment as to whether one is dealing with a dominant nodule or separate tumor nodules.[244] One should assign a separate grade to each dominant tumor nodule(s). Most often, the dominant nodule is the largest tumor, which is also the tumor associated with the highest stage and highest grade.

Grading variants and variations of adenocarcinoma of the prostate

Ductal adenocarcinomas should be graded as Gleason score 4 + 4 = 8, while retaining the diagnostic term of ductal adenocarcinoma to denote their unique clinical and pathologic features. There is no consensus on how mucinous (colloid) carcinoma should be scored.[238] Some authors suggest that a Gleason score of 8 is to be assigned, while others recommend ignoring mucin and grading the tumor based on the underlying architectural pattern. Small cell, sarcomatoid, and mucinous signet-ring cell carcinomas should not be assigned a Gleason grade. It has been suggested that the rare pleomorphic giant cell carcinoma of the prostate should be assigned a pattern 5 (Table 4.8).[238,271,272]

Table 4.8 Gleason grades in histologic variants and variations of prostate cancer

Variants
- Ductal carcinoma (pattern 4)
- Small cell carcinoma (no grade applies)
- Mucinous (colloid) carcinoma (pattern 4 (some pattern 3) vs grade according to underlying pattern)
- Mucinous signet-ring cell carcinoma (no grade applies)
- Sarcomatoid carcinoma (no grade applies)
- Pleomorphic giant cell (pattern 5)
- Adenosquamous carcinoma (uncertain)
- Lymphoepithelioma-like (no grade applies)
- Basal cell/adenoid cystic carcinoma (no grade applies)
- Urothelial carcinoma (involving prostatic ducts and acini with or without stromal invasion) (no grade applies)
- Squamous cell carcinoma (no grade applies)

Variations
- Atrophic features (underlying glandular pattern)
- Pseudohyperplastic (pattern 3)
- Glomeruloid (pattern 3 or pattern 4)
- Collagenous micronodules (mucinous fibroplasia) (underlying glandular pattern (most pattern 3))
- Focal acellular mucin extravasation (ignore mucin and use underlying glandular pattern)
- Foamy gland carcinoma (underlying glandular pattern (most pattern 3))
- Non-mucinous signet-ring cell features (cytoplasmic vacuoles) (underlying glandular pattern (most pattern 4 or 5))
- Hypernephroid (pattern 4)

Correlation between needle biopsy and radical prostatectomy Gleason scores

There have been several studies addressing the correlation between Gleason scores in needle biopsies and corresponding radical prostatectomy specimens. Although earlier studies used the thicker (14-guage) needle biopsies,[273,274] more recent series were based on thin-core (18-gauge) needles used in conjunction with biopsy guns attached to transrectal ultrasound. Sextant or other modes of systematic sampling is typically performed in the more current series. In a compilation of data on 3789 patients from 18 studies, exact correlation of Gleason scores was found in 43% of cases, and correlation plus or minus one Gleason core unit in 77% of cases.[254] Undergrading of carcinoma in needle biopsy is the most common problem, occurring in 42% of all reviewed cases. Importantly, overgrading of carcinoma in needle biopsies may also occur, but this was only found in 15% of cases. In general, adverse findings on needle biopsy accurately predict adverse findings in the radical prostatectomy specimen, whereas favorable findings on the needle biopsy do not necessarily predict favorable findings in the radical prostatectomy specimens, in large part due to sampling error.

Sources of discrepancies between needle biopsy and radical prostatectomy Gleason scores

Sampling error

Perhaps the most important factor is sampling error, which relates to the small amount of tissue removed by thin-core needle biopsies. The average 20-mm, 18-gauge core samples approximate 0.04% of the average gland volume (40 cc). The most common type of sampling error occurs when there is a higher grade component present within the radical prostatectomy specimen which is not sampled on needle biopsy.[261] This typically occurs when a needle biopsy tumor is graded as Gleason score 3 + 3 = 6. In the radical prostatectomy, there exists a Gleason pattern 4 which was not sampled on the biopsy, resulting in a prostatectomy Gleason 3 + 4 = 7.

In some instances, undergrading results from an attempt to grade very tiny areas of carcinoma, so-called minimal or limited adenocarcinoma.[262] Scores of minimal adenocarcinoma in needle biopsies show a reasonably strong correlation with radical prostatectomy scores, but the Gleason scores do not have the same power to predict extraprostatic extension and positive margin status as they do in non-minimal carcinomas.[262]

Overgrading can result from sampling error in cases where the high-grade pattern is selectively represented in needle biopsy. It may only represent a very minor element in the radical prostatectomy specimen. Even the same cancer focus may have different grades depending on the area sampled.

Borderline cases

The other source of discrepancy between biopsy and radical prosta-tectomy is borderline cases. In the description of the Gleason grading system, there are some cases that are right at the interface between two different patterns where there will be interobserver variability and possibly even intra-observer variability.[275]

Pathology error

Pathology error is most frequently seen when pathologists assign a Gleason score of ≤4 on a needle biopsy which in fact was Gleason score 5–6. Many pathologists undergrade needle biopsies by confusing quantitative changes with qualitative changes. When there is a limited focus of small glands of cancer on needle biopsy, by definition this is a Gleason pattern 3. Gleason pattern 3 consists of small glands with an infiltrative pattern. Biopsying truly low-grade adenocarcinoma of the prostate could not result in just a few neo-plastic glands but rather would be more extensive, as low-grade adenocarcinoma grows as nodules of closely packed glands rather than infiltrating in and amongst normal glands.

Undergrading may result from difficulty in recognizing an infil-trative growth pattern or failing to recognize the presence of small areas of gland fusion.[275]

Pathologists' education and experience

The pathologists' experience in grading thin-core needle biopsies can also influence overall correlation with radical prostatectomy results. With experience, pathologists recognize grading pitfalls, in particular, the fact that Gleason scores of 4 and lower are almost non-existent in needle biopsy situation. Furthermore, small areas of fusion in the presence of a predominantly grade 3 background are recognized and will yield a Gleason score of 7, which often correlates well with radical prostatectomy results.[276]

Intra-observer and inter-observer variability

Reproducibility studies can be categorized as intra-observer and inter-observer. For investigations of intra-observer agreement of

Table 4.9 World Health Organization (Mostofi) grading system

Grade	Definition
I	Well-differentiated glands with nuclei that show slight nuclear anaplasia
II	Gland formation but the nuclei show moderate nuclear anaplasia
III	Glands with marked nuclear anaplasia or tumors that are undifferentiated (do not form glands)

Gleason grades, exact agreement was reported in 43 to 78% of cases,[237,276] and agreement within plus or minus one Gleason score unit was reported in 72 to 87% of cases. Gleason wrote that he dupli-cated exactly his previous histologic scores approximately 50% of times. Highly variable levels of interobserver agreement on Gleason scores have also been reported, with a range of 36 to 81% for exact agreement and 69 to 86% for observers within plus or minus one Gleason score unit. Improvements in Gleason grading reproducibil-ity can be achieved by recognizing problematic areas and educating physicians via meetings, courses, website tutorials, and publications that specifically focus on the Gleason grading system.[237]

Grading systems other than Gleason

In addition to the Gleason score, another grading system may be used according to institutional preference (e.g. WHO, MD Anderson) but the Gleason score must be included to facilitate comparison of data[277] (Table 4.9).

Part 8

Clinical significance of treatment effects

Changes after androgen manipulation

The overall appearance of hormonally treated prostates is that of global senescence or involution of the gland (Table 4.10). The transition zone shows simplification of the glandular lobules, although the lobular configuration is retained. The ducts and acini are small, ovoid, round, or comma-shaped. There is no undulation of the epithelial border due to the presence of corrugations of the wall. The secretory cells have inconspicuous nucleoli, nuclear shrinkage, chromatin condensation, and cytoplasmic clearing. The basal cell layer is prominent and focal 'immature' squamous and basal cell hyperplasia is seen. Within the peripheral and central zones there is inconspicuous branching of the ducts and acini which appear dilated, star-shaped, and lined by flattened atrophic epithelium which is single-layered and seldom double-layered[278] (Figure 4.12(A)).

Prostatic intra-epithelial neoplasia

In the treated patients, PIN is generally observed in the peripheral zone and is localized in scattered ducts. Ferguson et al[279] and

---

Table 4.10 Pathologic findings in the prostate following androgen blockade. The changes affect normal prostate, PIN, and cancer

Architecture
- Prominent acinar atrophy with loss of hyperplastic glandular architecture in the transition zone
- Basal cell prominence and hyperplasia in benign prostate
- Squamous metaplasia, including the immature variant
- Decrease in extent of PIN
- Decrease in extent of prostatic adenocarcinoma with loss of luminal (acinar) architecture
- Decreased frequency of intraluminal crystalloids in prostatic adenocarcinoma

Cytology
- Cytoplasmic clearing and vacuolization
- Nuclear shrinkage
- Nuclear hyperchromasia
- Nuclear pyknosis with increased frequency of apoptotic bodies
- Lack of mitotic figures
- Loss of nucleolar prominence

Stroma
- Focal hypercellularity
- Focal lymphocytic/histiocytic infiltrate (including foamy, lipid-laden histiocytes)
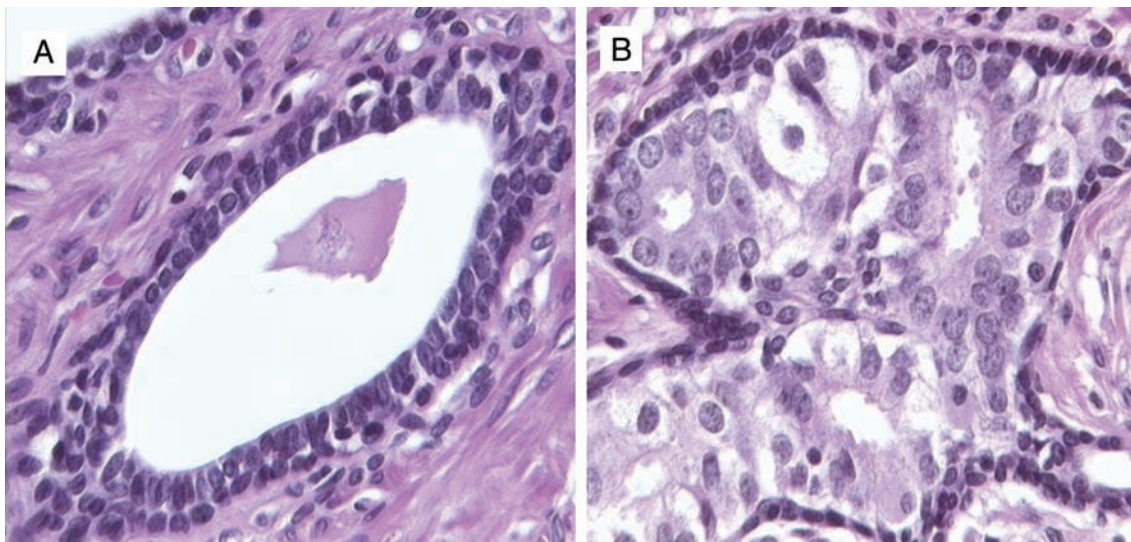
Figure 4.12
Changes after androgen manipulation. (A) Non-neoplastic acinus which appears dilated and lined by double-layered, flattened, atrophic epithelium. (B) Prostatic intraepithelial neoplasia. The cell lining shows a basal-cell layer which is recognizable. A certain degree of secretory cell type stratification is present. Crowding is less evident than in the untreated prostate. The cells have nuclear shrinkage, chromatin condensation and pyknosis, inconspicuous nucleoli, and cytoplasmic clearing.

Vaillancourt et al[280] demonstrated that the prevalence and extent of PIN are lower in treated glands. The cell lining shows a basal cell layer which is recognizable in most instances. A certain degree of secretory cell type stratification is always present. However, crowding is less evident than in the untreated prostate. The cells have nuclear shrinkage, chromatin condensation and pyknosis, inconspicuous nucleoli, and cytoplasmic clearing. Apoptotic cells are easily identifiable in all the cell type layers (Figure 4.12(B)). The duct and acinar lumen is always rich in cells: some are macrophages, some sloughed secretory cells with degenerative features, while others correspond to apoptotic cells. No clear post-treatment grading of PIN is possible.[281]

Blockade of 5-alpha-reductase with finasteride appears to have little or no effect on HGPIN, unlike other forms of androgen deprivation therapy. The incidence of HGPIN was unchanged in one study after one year of finasteride.[282]

Prostate cancer

Hormonal therapy results in a significant overall reduction in the volume of PCa when compared to untreated PCa in radical prostatectomy from clinically confined disease. Vaillancourt et al[280] reported a mean cancer volume of 4.66 cc in the untreated group versus 2.11 cc in the group of patients treated before surgery. However, calculating cancer volume in hormonally treated prostate is a very difficult task because residual disease is often present as scattered and multiple microscopic foci within a tissue section, which makes the calculation of tumor volume imprecise.

In general, histologic response seems to correlate with the tumor patterns and the Gleason grades observed before the androgen ablation therapy is started. Moreover, following total androgen ablation the morphologic changes are more pronounced than after hormonal monotherapy, i.e., LHRH analog or anti-androgen used alone. Residual PCa invading the prostatic capsule, periprostatic soft tissue, seminal vesicle, and metastatic to pelvic lymph nodes shows therapy-induced changes similar to adenocarcinomas confined within the prostate gland.[280,281,283–290]

The treated tumors, with acinar pattern (primary Gleason grade 1 to 3) in the biopsy before the androgen ablation therapy, show neoplastic acini which appear shrunken, a decreased frequency of intraluminal crystalloids, and areas of individual infiltrating tumor cells separated by abundant connective tissue. The epithelial tumor cells have cytoplasmic clearing and enlargement by coalescence of vacuoles and rupture of cell membranes. The nuclear chromatin shows different changes which range from a mild condensation – which barely allows the distinction between coarse chromatin granules (corresponding to heterochromatin) and finely dispersed chromatin (corresponding to euchromatin) – to a tightly condensed state close to that observed in apoptosis[291] (Figure 4.13). Similar to treated PIN, apoptotic bodies are easily identifiable in all epithelial cell layers as well as macrophages and sloughed epithelial cells in the lumina.[284] The hallmark of all the untreated adenocarcinomas is that the tumor nuclei are frequently multinucleolated, the nucleoli being prominent (mean diameter 1.47 µm), marginated, and with a perinuclear halo. In the treated cases the nucleoli become inconspicuous, without margination, and have a decreased mean diameter of 1.09 µm, the nucleolar diameter being below 1.0 µm in 20% of the tumors.[280] The treated tumors with pretreatment cribriform and solid/trabecular patterns (primary Gleason grade 4 and 5) show nuclear and cytoplasmic changes which appear less pronounced than in the acinar pattern.
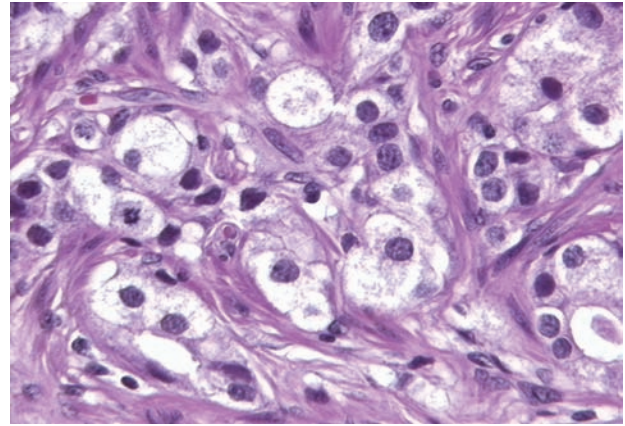
Figure 4.13
Prostate cancer. The neoplastic acini are shrunken. The epithelial tumor cells have cytoplasmic clearing and enlargement by coalescence of vacuoles and rupture of cell membranes. The nuclear chromatin shows different changes, which range from a mild condensation to a tightly condensed state close to that observed in apoptosis.

The stroma shows variable degrees of fibrosis, reduced capillary vascularity, and variable density of lymphocytic infiltrates, often intermingled with mast cells, plasma cells, and eosinophils. Infiltrates of foamy histiocytes, difficult to distinguish from PCa cells with clear cytoplasm, are sometimes present.[290] Periprostatic fibrosis, obscuring the normal cleavage plane and making the operation more difficult, is reported after hormonal therapy.[292] The longer patients receive hormonal therapy prior to surgery, the more fibrosis is observed around the prostate; up to now there are no detailed qualitative and quantitative histologic studies on the degree of fibrosis and its specific location. Based on a preliminary morphologic evaluation, it appears that there is an increased thickness of the fibrous connective tissue septa which usually transverse the adipose tissue surrounding the capsule. Focal areas in which the fatty tissue is totally obliterated by connective tissue are sometimes present laterally, posteriorly, and around the seminal vesicles. It cannot be excluded that this feature represents tumor-induced stroma in which cancer cells have regressed because of hormonal therapy.

Immunohistochemistry

In some cases residual tumor may be very focal, consisting only of isolated cells or cell clusters within prostatic stroma. Identification of these tumor foci is made more difficult by the presence of cellular, tumor-associated stroma and condensation of nuclear chromatin masking the prominent nucleoli of PCa cells. Significant difficulty may be encountered in separating minute clusters and single file ribbons of tumor cells from lymphocytes, myocytes, and fibroblasts. Small foci of residual PCa may also be missed in 4 to 15% of prostatectomy specimens.[280] Immunostaining with PSA and prostatic acid phosphatase can detect persisting tumor cells, though reduction in the intensity of staining following hormonal therapy limits their usefulness.[287] Cytokeratin immunohistochemistry may be necessary to confirm the presence of residual PCa, especially for pathologists with limited experience in these cases. Immunostaining with a low-molecular-weight cytokeratin, such as CAM 5.2 antibody,

will stain residual PCa cells, but the same cells will lack reactivity for high-molecular-weight cytokeratin 34ßE12.[283] The latter is expressed only in the basal cells of the prostate and not in secretory acinar epithelium, whether benign, premalignant, or malignant. Gleave et al.[293] found that 50% of the cases that exhibited no residual cancer on routine pathologic assessment had remaining foci of cancer discovered by immunostaining. Without the aid of additional step sections and immunostaining for cytokeratin these cases would have been reported as being stage pT0.[294] The usefulness of immunohistochemistry was shown also by Gould et al[295] in a study related to colloid pools and slit-like or hemangiopericytoma-like spaces devoid of lining cells occasionally present in the stroma of radical prostatectomy specimens subsequent to androgen deprivation therapy. These spaces showed strong immunostaining for A-80, an onco-developmental mucinous glycoprotein expressed only in preneoplastic and neoplastic prostatic cells, combined with sporadic cytokeratin reaction. The authors suggested that at least some of these spaces represent remnants of carcinomatous glands.[295]

Pathologic 'grading' of treated prostate cancer

A third of treated PCa cases are classified as high-grade (Gleason score 8 to 10), whereas, of the 56% that are of intermediate grade (Gleason score 5 to 7), the majority are Gleason score 7.[279,280,286] These percentages are much higher than expected in radical prostatectomy, i.e., there is a significant upgrading. Murphy's group[286] considered it likely that a shift to a higher grade in the prostate was largely an artifact of therapy-induced regression and due to the destruction of most of the tumor bulk, the residual tumor being often made of numerous isolated, single cells. These cells are non-viable and show marked therapy effects. According to others, higher grading could be explained by selective apoptosis of the more hormone-sensitive (low-grade) cells, leaving mainly higher-grade tumor cells in the specimen, and leading to an increase in Gleason score.[292] It has been argued that tumor upgrading is the result of selection of an androgen-insensitive clone, more likely to be poorly differentiated.[296] Data existing in the literature do not support this hypothesis.

Because of therapy-induced morphologic changes, grading of residual PCa, based on standard Gleason criteria, is not accurate and, therefore, discouraged.[287] Montironi et al[297] developed a Bayesian belief network (BBN) for the identification of PCa with hormone therapy changes from PCa with poor-to-no treatment effect and from untreated PCa. The BBN allowed the identification with high certainty of PCa with treatment-related changes from those either with poor/no treatment effect or untreated. There was complete agreement between the network results and the clinical information of androgen deprivation or not before surgery. There was a statistically significant correlation between pretreatment tumor grade and network results. Montironi et al concluded that a BBN for the evaluation of androgen-deprived PCa offers a descriptive classifier which is readily implemented in the evaluation of the degree of induced changes and allows the use of descriptive linguistic terms.

Van de Voorde et al[290] devised a regressive score system in a study on radical prostatectomy specimens from patients with localized PCa treated either with flutamide or estramustine phosphate (a hybrid molecule combining an estrogen moiety and an alkylating agent). The regressive score was based on the evaluation of nuclear pyknosis, cytoplasmic vacuolization, degree of fibrosis, and interstitial lymphocytic infiltration. Each of these four features had different outcomes expressed in numbers. They found that the score values obtained from the patients treated with estramustine phosphate were higher than those from patients treated with flutamide. This system is similar to that published by Montironi et al.[297] The main difference is that the network from the latter group gives the level of confidence on the regression grade.

Effect of androgen ablation on pathologic stage and resection limit status of prostate cancer

There is conflicting evidence regarding pathologic downstaging, with some studies suggesting benefit and others no benefit of androgen manipulation before radical prostatectomy. The least controversial aspect of neoadjuvant therapy is its impact on surgical margins.[298] Most series, whether prospective and controlled or not, and whatever the type of hormonal deprivation, have shown that neoadjuvant therapy in clinical T2 tumors is associated with a 20–25% decrease in positive margins in radical prostatectomy specimens.[292] In patients with clinical T3 tumors, the effects of neoadjuvant therapy on positive margins are less clear.

Changes after radiation therapy

Prostatic intra-epithelial neoplasia

To date there are only few papers on the effect of radiation therapy (RT) on high-grade PIN. The most recent reference to this was made by Cheng et al[299] in a paper on the prevalence and distribution of PIN in salvage radical prostatectomy specimens after radiation therapy. It was found that PIN identified after RT usually retains the features characteristic of untreated PIN. It is readily recognized in the radical prostatectomy specimens. The salient pathologic features include nuclear crowding, nuclear overlapping and stratification, nuclear hyperchromasia, and prominent nucleoli. The basal cell layer is still present, but fragmented. The most common patterns of PIN are tufting and micropapillary, similar to those reported by Bostwick et al.[15] Basal cell prominence and secretory cell cytoplasm vacuolization may be seen in high-grade PIN after RT.

The main differential diagnosis of high-grade PIN after RT is atypical basal cell hyperplasia. The proliferation of basal cells in atypical basal cell hyperplasia is often eccentrically located with partial involvement of acini, retaining the overlying columnar or cuboidal secretory cells. These atypical basal cells have enlarged nuclei and nucleoli, fine powdery chromatin, occasional nuclear grooves, and an absence of apocrine blebs. Nuclear 'bubble' artifact or intranuclear vacuoles may be seen. In difficult cases, the use of immunostaining for high-molecular-weight keratin may be helpful in distinguishing atypical basal cell hyperplasia from high-grade PIN. Data on the effect of RT on intraductal carcinoma are not available yet.

Cheng et al also gave information about the prevalence and extent of PIN after RT.[299] In particular, they found small-volume PIN (mean 0.12 cm³) in 62% of patients. By comparison, Qian et al[16] noted that 82% of step-sectioned prostate glands removed for prostate cancer had coexistent untreated high-grade PIN, with an

average volume of 1.32 cm³. Akakura et al[300] found a higher incidence (70%) of PIN after RT than Cheng et al.[299] These two groups suggested that RT affects non-invasive precursor lesions in a manner analogous to that apparent in ductal carcinoma in situ of the breast. A different opinion was expressed by Wheeler, who concluded that insufficient information existed to determine whether RT affected the incidence and extent of PIN.[301]

The long-term efficacy of radiation treatment may depend on eradication of cancer as well as precancerous lesions that may otherwise lead to evolution of secondary metachronous invasive cancers. Identification of residual or recurrent cancer portends a worse prognosis. The questions remain whether recurrent cancer after irradiation is due to regrowth of incompletely eradicated tumor or progression from incompletely eradicated HGPIN. Further studies of salvage prostatectomy specimens and post-RT needle biopsies are justified in an attempt to establish the significance of HGPIN as a source of long-term treatment failure among these patients. If HGPIN is associated with treatment failure, adjuvant chemoprevention strategies that ablate this lesion or coexistent carcinoma may reduce the risk of late cancer recurrence.

Prostatic cancer

Radiation therapy can be given as either external beam or interstitial seed implants, or as a combination of the two. The histologic effects on the cancer are identical. After radiation therapy the prostate gland is usually small and hard. Radiation therapy affects prostate cancer variably, with some glands showing marked radiation effect and others showing no evidence of radiation damage. Architecturally, carcinomas showing treatment effects typically lose their glandular pattern, resulting in clustered cells or individual cells. Cytologically, the cytoplasm of the tumor cells is pale, increased in volume, and often vacuolated. There is often a greater variation of nuclear size than in non-irradiated prostate cancer and the nuclei may be pyknotic or large with clumped chromatin. Nucleoli are often lost.[302–308] Paradoxically the nuclear atypia in prostate carcinoma showing radiation effect is less than that seen in radiation atypia of benign glands. The stroma is often sclerosed, particularly following radioactive seed implantation. In the latter the stromal hyalinization is often sharply delineated. Biopsy findings predict prognosis with positive biopsies showing no treatment effect having a worse outcome than negative biopsies, and cancer with treatment effect having an intermediate prognosis.[309]

Immunohistochemistry

By immunohistochemistry, tumor cells with treatment effect are usually positive for PAP and PSA. These antibodies along with pancytokeratins are very helpful to detect isolated residual tumor cells, which can be overlooked in H&E stained sections. Immunohistochemistry with antibodies against 34βE12 or p63 is useful to distinguish cancer from normal with effects due to radiation therapy (Figures 4.14(A) and (B)).

Pathologic 'grading' of treated adenocarcinoma

Following radiation therapy, prostatic biopsy should be diagnosed as no evidence of cancer, cancer showing no or minimal radiation effect, or cancer showing significant radiation effect, or a combination of the above. Although there exist various systems to grade radiation effects, these are not recommended for routine clinical practice.
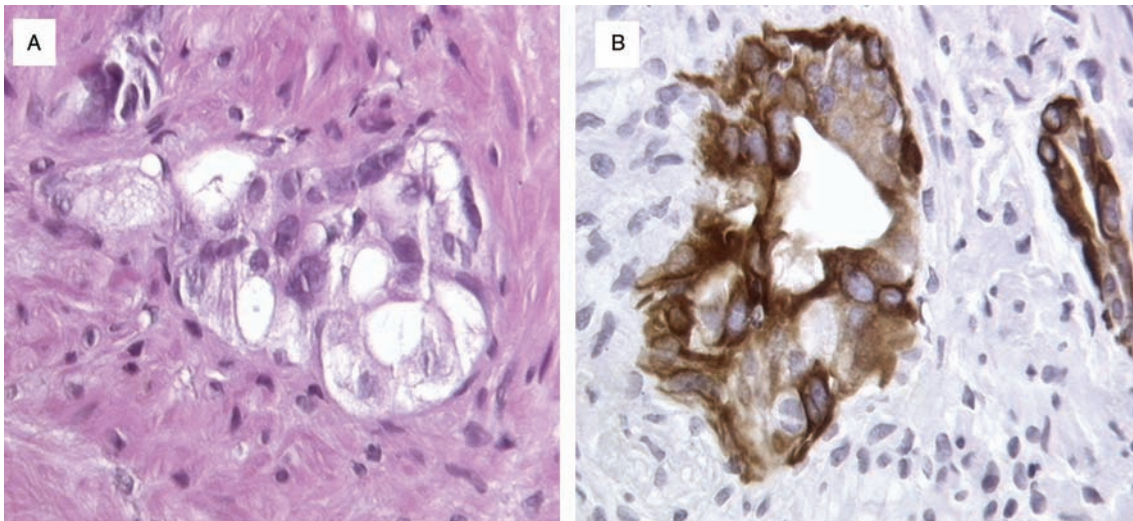
Figure 4.14
Changes after radiation therapy. (A) Acinus suspicious for adenocarcinoma. Loss of glandular pattern. Cytologically, the cytoplasm of the tumor cells is pale, increased in volume and often vacuolated. (B) Immunohistochemistry with an antibody against 34βE12 is useful to distinguish cancer from normal cells with effects due to radiation therapy.

Part 9

Prognosis of prostate cancer

Knowledge of prognostic factors in cancer has broad applications in areas of patient care, research, and in cancer control programs (Table 4.11). Prognostic factor assessment in a given cancer allows appropriate selection of diagnostic treatment plans. It allows for prediction of outcome in individual patients and also general outcomes following a therapeutic intervention. Prognostic factors are also important for education of patients and caregivers.

In the research area, knowledge of prognostic factors allows appropriate stratification of patients in clinical trials to properly assess and compare therapeutic outcomes. Furthermore, it defines subgroups with predictably poor outcomes for other novel experimental therapies and can identify candidates for possible organ preservation trials.

In broader terms, an understanding of prognostic factors is used in cancer control programs to plan resources and to assess screening programs. Prognostic factors are also important in the introduction and monitoring of clinical practice guidelines and for public education about oncology.[1]

Prostate biopsies

The information provided in the surgical pathology report of a prostate needle biopsy with carcinoma has become critical in the subsequent management and prognostication of the cancer. The surgical pathology report should thus be comprehensive and yet succinct in providing relevant information consistently to urologists,

---

Table 4.11 Application of prognostic factors

Patient care
- Select appropriate diagnostic tests
- Choose appropriate treatment plan
- Predict outcome for individual patient
- Establish informed consent
- Assess outcome of therapeutic intervention
- Select appropriate follow-up monitoring
- Provide patient and caregiver education

Research
- Prognostic stratification
- Design future studies

Cancer control programs
- Plan resource requirements
- Assess the impact of screening programs
- Introduce and monitor clinical practice guidelines
- Explain variation in observed outcomes
- Provide public education

Table 4.12 Prognostic factors in prostate biopsies with cancer

- Location and distribution of tumor
- Histopathologic type
- Gleason score including primary and secondary pattern
- Extent of involvement
- Local invasion: extraprostatic extension and seminal vesicle involvement
- Perineural invasion: extent (focal vs multifocal) and diameter of nerve bundles
- Lymphovascular invasion

---

radiation oncologists and oncologists, and, thereby, to the patient[310,311] (Table 4.12).

Histologic type

Since acinar adenocarcinoma is the overwhelming histologic type of cancer in needle biopsy specimens, it is not necessary to specify such cancers as acinar or conventional type in pathology reports.

Carcinomas of the prostate with architectural or cytologic variations such as atrophic, pseudohyperplastic, hypernephroid, etc., are descriptive terms used to describe variations in prostate cancer to help pathologists recognize diagnostic pitfalls, but have no known prognostic significance. They may be commented upon in a microscopic description and do not deserve specific mention in the final diagnosis.

Several variants of prostate cancer have been described, including ductal, mucinous, signet-ring cell, adenosquamous, small cell carcinoma, and sarcomatoid carcinoma.[240] The former three are diagnoses tenable only on examination of radical prostatectomy or transurethral resection specimens. If seen in needle biopsy specimens the diagnostic terminology used must be: adenocarcinoma of prostate with ductal features; adenocarcinoma of prostate with signet-ring cell features; and adenocarcinoma of prostate with mucinous differentiation. Small cell carcinoma, sarcomatoid carcinoma, and adenosquamous carcinoma may be diagnosed on needle biopsies. There are no formal studies that have demonstrated that the presence of these histologic variants in needle biopsies is of prognostic or predictive importance, although the often aggressive outcome associated with such tumors suggests the value of this exercise.

Cancer grade

The Gleason grading system is recommended as the international standard for grading prostate cancer (see *Part 7 Current clinical practice*

of Gleason grading of prostate cancer). The WHO nuclear grading system should be used in addition to the Gleason scheme, but, in practice, is rarely or never reported.[244]

Extent of involvement of needle core (tumor volume)

The amount of tumor in prostate needle cores is an important pathologic parameter that must be reported in needle biopsies (Table 4.13). The extent of involvement of needle cores by prostatic adenocarcinoma has been shown to correlate with the Gleason score, tumor volume, surgical margins, and pathologic stage in radical prostatectomy specimens.[255,312] The extent of needle core involvement including bilateral involvement has also been shown to predict biochemical recurrence, post-prostatectomy progression, and radiation therapy failure in univariate and often in multivariate analysis.[255,312–314] It is a parameter included in some recent nomograms created to predict pathologic stage and seminal vesicle invasion after radical prostatectomy and radiation therapy failure.[313,315–317]

The amount of cancer in a biopsy specimen depends on many factors, including prostate volume, cancer volume, cancer distribution, technical procedure, number of biopsy cores obtained, and cohort of patients being evaluated.

There is a lack of consensus in the literature as to the best method of reporting the extent of tumor involvement. The report should provide the number of involved cores (if possible it should include percentage of cores involved). In addition, one or both of the following more detailed methods of tumor extent should be performed. One method is to report the linear length of cancer in mm (total tumor length in all biopsies; longest single length of tumor)[318] (Figure 4.15). The other method is to provide a percentage estimate of involvement of each of the cores derived by visual estimation (overall percentage of cancer in all biopsies, percentage of each core involved; reporting the percentage of cancer involvement in increments of 5 or 10% is appropriate).[319] The correlation is with greater involvement of the cores. While the correlation for high tumor burden in needle biopsies is directly proportional to the likelihood of an adverse outcome, low tumor burden in needle biopsies is not necessarily an indicator of low volume and low-stage cancer in the prostatectomy specimen.[320]

One problem encountered with this otherwise straightforward method is when there is extreme fragmentation of the needle biopsy specimen, making assessment of the number of cores and the percentage of cancer within each core difficult. In case of highly fragmented tissue this may be overcome by providing a composite (global) percentage of involvement of cancer in all needle biopsy tissue, and this may be a slightly more accurate correlate of the amount of cancer in the prostate gland itself.

Bilateral cancer, which indicates multifocality, is indirectly suggestive of greater tumor volume. This parameter is easily deduced from the pathology report findings of each of the cores submitted. In patients not subsequently treated by radical prostatectomy, this is a critical factor in assigning 'pathologic stage'.

Local invasion (location of carcinoma)

Routine biopsy sampling may occasionally contain extraprostatic fat or seminal vesicle tissue. If cancer is noted to involve these structures, the finding would indicate pT3 disease (Figure 4.16). The presence of seminal vesicle invasion or extraprostatic fat involvement in the staging biopsy is highly correlative of similar findings at radical prostatectomies. Extraprostatic fat invasion at needle biopsy is highly predictive of biochemical recurrence (79% compared to 43% failure rate in cases with extraprostatic extension not detected by needle biopsy).

Only exceptionally rarely is fat present within the normal prostate. Hence, tumor in adipose tissue in a needle biopsy specimen can safely be interpreted as extraprostatic extension.[319,321] Ganglion cells and skeletal muscle involvement by tumor is not equivalent to extraprostatic extension as they may both be found frequently within the prostate.

Distinction between the seminal vesicle epithelium and ejaculatory duct epithelium may be impossible in limited samples, although occasionally the seminal vesicle can be distinguished if its smooth

---

Table 4.13 Diagnostic reporting of amount of tumor in needle cores

- ■ Number of cores involved
- ■ Amount of cancer in biopsy (either method optional)
  - — Linear measurement in mm (total tumor length in all biopsies, longest single length of tumor)
  - — Percent of sampled tissue (overall % of cancer in all biopsies, % of each core involved)
- ■ Bilaterality
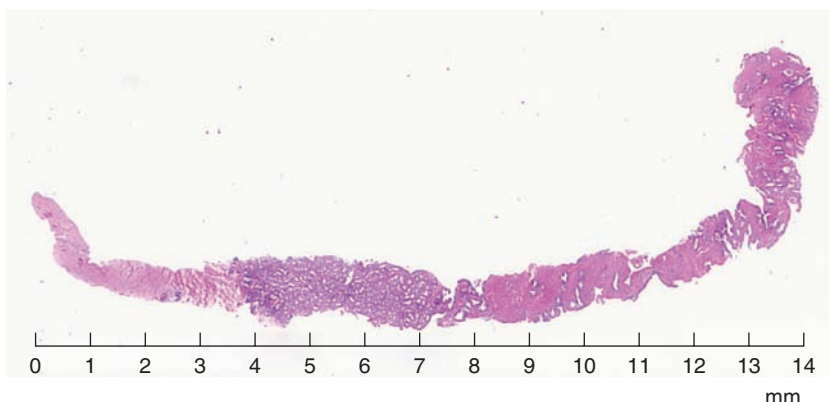
Figure 4.15
Prostate biopsy with cancer. A ruler is also present. Extent of involvement of needle core is equal to 3 mm.
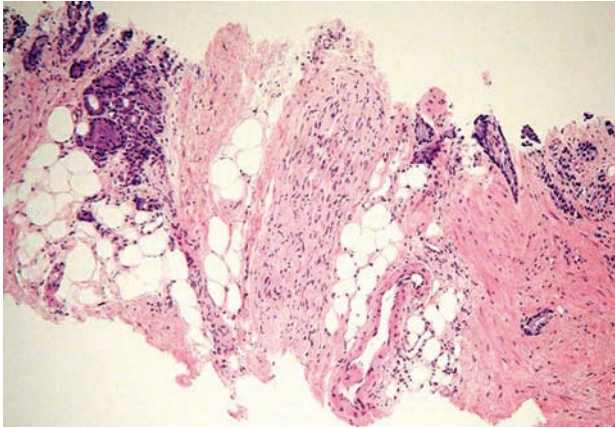
Figure 4.16
Cancer involves extraprostatic fat.

Figure 4.17
Perineural invasion.

Figure 4.18
Microvascular invasion. (Insert: immunohistochemical stains directed against endothelial cells such CD34).

muscle wall is present. In contrast, ejaculatory duct epithelium has a rim of fibrous tissue that is rich in thin blood vessels. If the distinction between seminal vesicle tissue/ejaculatory duct is not feasible, diagnostic terminology such as 'adenocarcinoma of the prostate with invasion of seminal vesicle/ejaculatory duct tissue' may be used.

In seminal vesicle or extraprostatic fat targeted biopsies, it is important to not only diagnose cancer, but also to determine whether or not the targeted tissue is represented. In a positive biopsy, if the intended tissue is not present and its absence not specified in the report, there is a high likelihood of misinterpretation of locally advanced disease which is not present. Also, seminal vesicle containing/targeted biopsies should demonstrate tumor within the muscular wall.

Perineural invasion

Perineural, circumferential, or intraneural invasion is defined as the presence of prostate cancer juxtaposed intimately along, around, or within a nerve (Figure 4.17). Other descriptors of perineural invasion that may strengthen the prognostic significance of this parameter include extensive (multifocal) perineural invasion and greater nerve diameter.[322] Involvement of nerves present within adipose tissue (extraprostatic nerves) by cancer indicates extraprostatic extension and deserves notation in the pathology report when present.

Although perineural invasion in needle biopsy specimens is not an independent predictor of prognosis when the Gleason score, serum PSA, and extent of cancer are factored in, most studies indicate that its presence correlates with extraprostatic extension (38–93%).[323–325] Recent data suggest that this finding may independently predict lymph node metastasis and post-surgical progression.[324,326] This parameter may also be used to plan nerve-sparing surgery.[327] Some of the data from the radiation oncology literature suggest that it is an independent risk factor for predicting adverse outcome after external beam radiation therapy and in patients with high Gleason score and perineural invasion, adjuvant hormonal therapy or dose escalation has been advocated.[324,328]

Vascular/lymphatic invasion

Microvascular invasion consists of tumor cells within endothelial-lined spaces (Figure 4.18). The presence of a cellular reaction in the adjacent stroma is not required for diagnosis. Also, we do not differentiate between vascular and lymphatic channels because of the difficulty and lack of reproducibility among different observers by routine light microscopic examination.[329] Microvascular invasion may be confused with fixation-associated retraction artifact of acini. Immunohistochemical stains directed against endothelial cells such as factor VIII-related antigen, *Ulex Europaeus*, CD31, or CD34 may increase the detection rate[329] (Figure 4.18, insert).
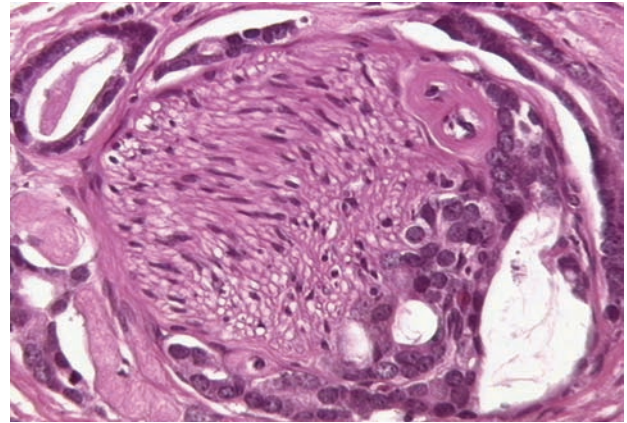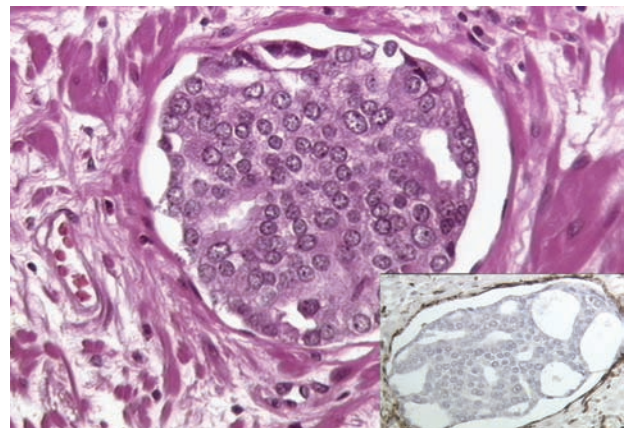
Since lymphovascular invasion as studied in radical prostatectomy specimens correlates with lymph node metastasis, biochemical recurrence, and distinct metastasis, its presence in the needle biopsy is likely to have similar correlations. This feature is very rarely seen in needle biopsy specimens. This finding should be reported in needle biopsy specimens only if identified.[330,331]

Prognostic molecular markers

Other preoperative factors may improve the predictive accuracy for pathologic stage, including neuroendocrine (NE) differentiation (see also Parts 6 and 11), nuclear DNA content, and microvessel density[332,333] (Table 4.14).

Table 4.14 Biomarkers of potential prognostic usage in prostate cancer*

Proliferation/apoptosis	Growth factors (GF)
Ki-67 (mib-1)	epidermal GF : Her2/neu
PCNA	insulin-like GF
bcl-2	fibroblast GF
high mobility protein I (Y)	transforming GF
	endothelial GF
Enzymes	platelet GF
5 alpha-reductase	neural GF
telomerase	
racemase	Microvessel density
12-lipoxygenase	
metalloproteinases +	Genetic/molecular
inhibitors	DNA ploidy
	chromosome 7,8 gains/losses
Proteins	p53
cytokeratins	p21
cell adhesion marker	c-myc expression
E-cadherin	Rb protein
relaxin	androgen receptor gene
activin	mutation
inhibin	KAT 1 suppressor gene
androgen receptor	

*This list is not meant to be comprehensive but presents some general categories of biomarkers and specific examples where research has been undertaken.

Nuclear DNA content

DNA ploidy analysis of prostate cancer by flow cytometry and digital image analysis provides important prognostic information that supplements histopathologic examination. Controversy exists, however, about whether it is a significant predictor above Gleason score in multivariate analysis. DNA ploidy pattern correlates with cancer grade, tumor volume, and stage.[334] Most low-stage tumors are diploid, and high-stage tumors are non-diploid, but many exceptions occur.[335]

Microvessel density

A significant increase in microvessel density (MVD) occurs in prostatic intraepithelial neoplasia[336] and carcinoma compared with normal prostatic tissue.[336] Mean blood vessel count is higher in tumors with metastases than in those without metastases,[337] and most studies,[336] but not all,[338] show a correlation with pathologic stage. MVD appears to be an independent predictor of cancer progression in some studies.[338,339] The cumulative data suggest that increased MVD contributes to extraprostatic spread of adenocarcinoma, perhaps by facilitating microvascular invasion.

Other molecular markers

The discovery of new molecular markers that in a needle biopsy setting are of prognostic significance is very much the need of the hour.[311,333]

After radical prostatectomy and pelvic lymphadenectomy

The pathology report should include clinically relevant information as well as provide clinically useful information derived from the macroscopic examination and microscopic evaluation of the radical prostatectomy specimens and pelvic lymph nodes (Tables 4.15 and 4.16). Separately, some other extensively studied biological and clinical factors, whose importance remains to be validated in statistically robust studies, may be recorded.

Table 4.15 Clinical information

1. Patient identification
   a. Identification number
   b. Name
   c. Age (birth date)
2. Clinical information
   a. Relevant history and preoperative findings (previous diagnosis, treatment, includes PSA, imaging)
   b. Operative findings
   c. Anatomic site(s) of specimen(s)
   d. Procedure
      ■ Retropubic procedure
         – nerve sparing
         – standard radical
      ■ Perineal procedure
      ■ Others
3. Responsible physician(s)

Table 4.16 Required reporting for radical prostatectomy specimen

1. Histologic type of carcinoma
2. Gleason grade (when untreated) (if 3 patterns are present, record the predominant and second most common patterns; the tertiary pattern should be recorded in a comment if higher than primary and secondary patterns)
3. Tumor location
4. Margin status
   Extent if positive
   Focal
   Non-focal
   Location of positive margins
   Specify status of following margins: bladder neck, apical, vas deferentia (optional)
   Nature of positive margins
   In area of extraprostatic extension
   Iatrogenic (pT2+)
5. Extraprostatic extension (EPE)
   Extent of EPE
   Focal
   Non-focal
   Location of EPE
6. Vascular invasion
7. Seminal vesicle invasion
8. Tumor quantitation*
9. Pathologic staging (pTNM)
10. Comments: correlation with intra-operative consultation; correlation with other specimens, as appropriate; correlation with clinical information, as appropriate

* Some indication as to tumor extent is advised, even if a subjective 'minimal', 'moderate', or 'extensive'. Optional techniques include more objective quantification, such as 'tumor percentage within the gland'.

Histologic type of cancer

In recent years, a number of new and unusual histologic variants or subtypes have been identified. These variants represent the spectrum of changes which can occur in adenocarcinoma. The biological behavior of many of these variants may differ from typical adenocarcinoma and proper clinical management depends on accurate diagnosis and separation from tumors arising in other sites. It is recommended that subtypes, such as small cell, ductal, and mucinous, should be reported if they are noted histologically. Mixtures of different histologic types should be indicated.[340]

Histologic grade of cancer

The Gleason score assigned to the tumor at radical prostatectomy is the most powerful predictor of progression following radical prostatectomy[235,236,259,267,341] (see *Part 7 Current clinical practice of Gleason grading of prostate cancer*).

Staging

The protocol recommends the use of the TNM staging system for carcinoma of the prostate of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC), as shown below.[342,343] The most recent revision was published in 2002. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible (Table 4.17). The prefix symbol 'p' refers to the pathologic classification of the TNM

(pTNM), as opposed to the clinical classification (Table 4.18). Pathologic classification is based on gross and microscopic examination. By AJCC/UICC convention, the designation 'T' of the TNM classification refers exclusively to the first resection of a primary tumor. Therefore, pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category; pN entails removal of nodes adequate to validate lymph node metastasis; and pM implies microscopic examination of distant lesions (Tables 4.19 and 4.20).

Tumor remaining in a resection specimen following previous (neoadjuvant) treatment of any type (radiation therapy alone, chemotherapy alone, or any combined modality treatment) is codified by the TNM using a prescript 'y' to indicate the post-treatment status of the tumor (e.g., ypT1). The classification of residual disease may be a predictor of postoperative outcome. In addition, the ypTNM classification provides a standardized framework for the collection of data needed to accurately evaluate new neoadjuvant therapies.

Tumor that is locally recurrent after a documented disease-free interval following surgical resection is classified according to the TNM categories, but modified with the prefix 'r' (e.g., rpT1).

Table 4.17 Primary tumor, clinical (cT) (2002 revision)*

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- T1: Clinically inapparent tumor not palpable or visible by imaging
  - T1a: Tumor incidental histologic finding in 5% or less of tissue resected
  - T1b: Tumor incidental histologic finding in more than 5% of tissue resected
  - T1c: Tumor found in one or both lobes by needle biopsy, but not palpable or visible by imaging (elevated PSA)
- T2: Tumor confined within the prostate
  - T2a: Tumor involves one half of one lobe or less
  - T2b: Tumor involves more than half of one lobe, but not both lobes
  - T2c: Tumor involves both lobes
- T3: Tumor extends through the prostatic capsule*
  - T3a: Extracapsular extension (unilateral or bilateral)
  - T3b: Tumor invades the seminal vesicle(s)
- T4: Tumor is fixed or invades adjacent structures other than the seminal vesicles, bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall

* Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2. Tumor extension into periprostatic soft tissue, as opposed to organ confined cancer (T2), is T3.

Table 4.18 Primary tumor, pathologic (pT) (2002 revision)

(There is no pathologic T1 category)
- pT2: Organ confined*
  - T2a: Tumor involves one half of one lobe or less
  - T2b: Tumor involves more than half of one lobe, but not both lobes
  - T2c: Tumor involves both lobes
- pT3: Extraprostatic extension
  - pT3a: Extraprostatic extension
  - pT3b: Seminal vesicle extension
- pT4: Invasion of bladder,** rectum

* Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2. Tumor extension into periprostatic soft tissue, as opposed to organ confined cancer (T2), is T3.
** See text.

Table 4.19 Regional lymph nodes (N)

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Metastasis in regional lymph node or nodes

Table 4.20 Distant metastasis (M) (when more than one site of metastasis is present, the most advanced category (pM1c) is used)

- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis
  - M1a: Non-regional lymph node(s)
  - M1b: Bone(s)
  - M1c: Other site(s)

Extent of local invasion

This includes extraprostatic extension (pT3a) and seminal vesicle involvement (pT3b).

Histologically, the prostatic capsule is not well defined. In areas there may appear to be a fibrous or fibro-muscular band at the edge of the prostate, although in other areas normal prostatic glands extend out to the edge of the prostate without any appearance that there is a capsule. Because the prostate lacks a discrete capsule, the term 'extraprostatic extension' (EPE) has replaced 'capsular penetration' to describe tumor that has extended out of the prostate into periprostatic soft tissue[243,344] (Figures 4.19(A) and (B)). Tumor abutting on or admixed with fat constitutes extraprostatic extension. EPE may also be reported when tumor involves perineural spaces in the neurovascular bundles, even in the absence of periprostatic fat involvement.

The group from Baylor has been one of the few proponents of assigning levels to designate the extent of tumor going through the 'capsule'.[241] As there is no well-defined prostatic capsule, it is hard to imagine how one would reproducibly diagnose tumor going into but not through the 'capsule'.

Difficulty in diagnosing EPE arises when tumor extends out of the prostatic gland and induces a dense desmoplastic response in the periprostatic adipose tissue. This is most commonly seen in prostatectomy specimens obtained after endocrine neoadjuvant therapy. Because of the desmoplastic response, it can be difficult to judge whether the tumor has extended out of the gland or is within the fibrous tissue of the prostate. The best way of assessing whether extraprostatic extension has occurred is to look at the adjacent edge of the prostate on scanning magnification where there is no tumor and follow the edge of the gland to the area in question to see whether the normal rounded contour of the gland has been altered by a protuberance corresponding to extension of tumor into the periprostatic tissue.

In certain locations, such as the anterior prostate and bladder neck regions, there is a paucity of fat. In these locations EPE is determined when the tumor extends beyond the confines of the normal glandular prostate. At the apex, tumor admixed with skeletal muscle elements does not constitute extraprostatic extension.[345]

The degree of extraprostatic extension varies from only a few glands outside the prostate to cases with more extensive extraprostatic spread. The amount of EPE carries prognostic importance. Different ways have been used to define the amount of EPE. If it is equal to, or less than two high-power (40 $\times$) microscopic fields, then EPE is focal.[243] Any amount in excess of two high-power fields is considered to be either non-focal or extensive.

Seminal vesicle invasion (SVI) is defined as cancer invading into the muscular coat of the seminal vesicle[346,347] (Figure 4.20). SVI has been shown in numerous studies to be a significant prognostic indicator.[348–351] Three mechanisms by which prostate cancer invades the seminal vesicles were described by Ohori et al[347] as:

1. by extension up the ejaculatory duct complex;
2. by spread across the base of the prostate without other evidence of EPE or involvement from tumor invading the seminal vesicles from the periprostatic and periseminal vesicle adipose tissue; and
3. as an isolated tumor deposit without continuity with the primary prostate cancer tumor focus.

While in most cases, SVI occurs in glands with EPE, the latter cannot be documented in a minority of these cases. Many of these patients had only minimal involvement of the seminal vesicles, or involving only the portion of the seminal vesicles that is at least partially intraprostatic. Patients in this category were reported to have a favorable prognosis, as for otherwise similar patients without SVI.[346]

Several improvements of the 6th edition TNM staging of prostate cancer were recommended (Table 4.21).[241]

Positive surgical margins

Patients with positive margins have a significantly increased risk of progression as compared to those with negative margins.[352] There are two causes for positive margins (Figure 4.21):

- Non-iatrogenic causes of positive margins: positive margins can result from a failure to widely excise extraprostatic extension of tumor.
- Capsular incision: one cause of a positive resection margin is transection of intraprostatic tumor (capsular incision). These cases

pT2a

pT3a
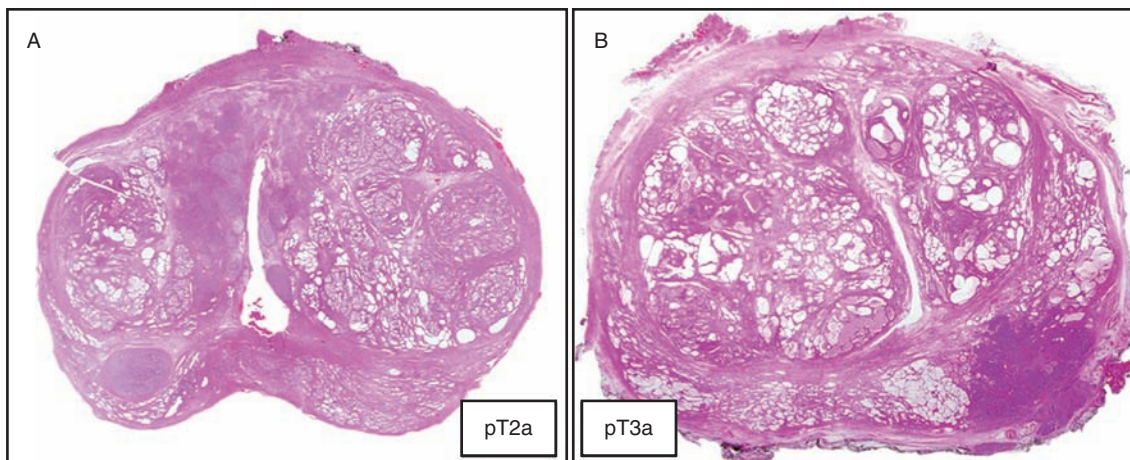
Figure 4.19

(A) Cancer is still within the peripheral zone of the prostate. (B) Cancer extends to the periprostatic fat tissue (EPE).
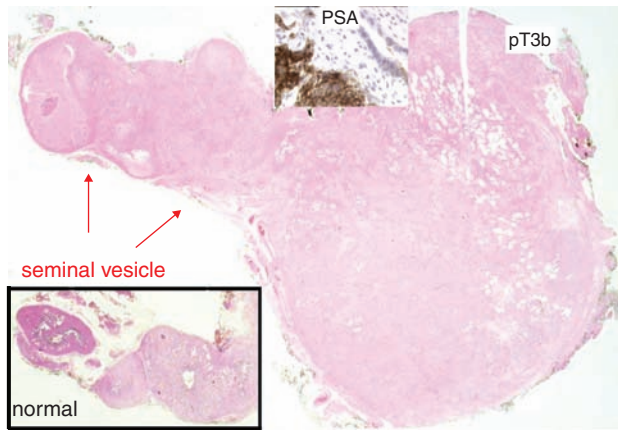
Figure 4.20
Seminal vesicle invasion. PSA immunostain confirms that it is cancer originating from the prostate. A normal seminal vesicle is shown in the insert.

Table 4.21 Proposed modifications to the 6th edn TNM staging for prostate cancer[241]

6th Edition	Proposed modifications
pT2a, pT2b, pT2c Organ-confined (stratified by how much prostate involved)	pT2 Organ-confined (regardless of extent)
pT3a Extraprostatic extension (not stratified by extent)	pT3a$_1$ Focal extraprostatic extension
pT3b Seminal vesicle invasion	pT3a$_2$ Non-focal extraprostatic extension
	pT3b Seminal vesicle or microscopic bladder neck invasion
pT4 Includes bladder neck invasion	pT4 Invasion of adjacent organs (excluding microscopic bladder neck involvement)
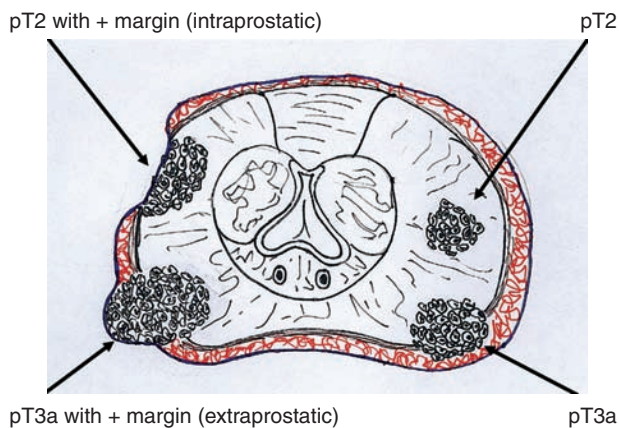
Figure 4.21
Diagram showing examples of pT2 (cancer confined within prostate), pT3a (cancer with extraprostatic extension, EPE), pT2 with + margin (capsular incision: positive resection margin due to transection of intraprostatic tumor), and pT3a with + margin (non-iatrogenic cause of positive margins: positive margins due to failure to widely excise extraprostatic extension of tumor). Reproduced with permission from Montironi et al. Handling and pathology reporting of radical prostatectomy specimens. Eur Urol 2003; 44: 626–36.

should be designated as pathologic stage T2X, denoting that elsewhere the tumor is organ-confined, yet one cannot determine whether there is extraprostatic extension in the region of capsular incision as the edge of the prostate has been left in the patient.

Surgical margins should be designated as 'negative' if tumor is not present at the inked margin and as 'positive' if tumor cells touch the ink at the margin (Figure 4.22). Positive surgical margins should not be interpreted as extraprostatic extension. If the surgical margin is positive, the pathologist should state this explicitly, although this finding is not relied upon for pathologic staging. The examining pathologist should be aware of false positive margins due to the penetration of ink into cracks present on the external surface. The main cause for discrepancy in the definition of a positive margin is seen in situations in which cancer was very close but not clearly touching the inked margin or when the color used to identify the margin appeared very pale.

The specific locations of the positive margins should be documented and there should be some indication (e.g. number of positive blocks, linear extent in millimeters) of the extent of margin positivity. The apex should be closely examined because of its unusual susceptibility to positive margins.[152,345,352]

There is no full consensus on the definition of the T category in the situation in which the prostate base/bladder neck is involved and the margin is positive. This problem is linked to the fact that the basal prostatic stroma blends imperceptively into the bladder neck musculature and, therefore, to the difficulty in defining the exact transition point from prostate base to bladder neck, even though the latter is composed of distinct large bundles of smooth muscle fibers.[353] Microscopic involvement of bladder neck muscle fibers in radical prostatectomy specimens should be defined as pT4.[354] Others[355] think that the microscopic involvement of bladder neck muscle fibers in radical prostatectomy specimens should not be equated with a pT4 designation, the latter generally requiring gross involvement of the bladder neck (Table 4.21).

Tumor remaining in a patient after therapy with curative intent (e.g., surgical resection) is categorized by a system known as R classification (Table 4.22). This classification may be used by the surgeon to indicate the known or assumed status of the completeness of the surgical resection. For the pathologist, the R classification is relevant only to the margins of surgical resection specimens; patients with tumor involving the resection margins on pathologic examination
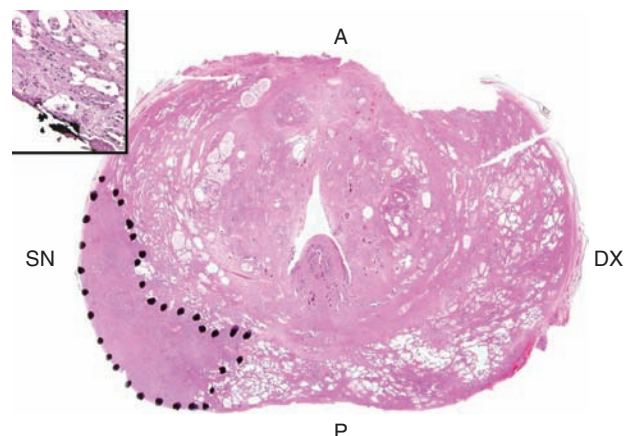
Figure 4.22
Cancer is present in the peripheral zone. The insert shows that cancer reaches the inked margin.

Table 4.22 Residual tumor in the patient

- RX: Presence of residual tumor cannot be assessed
- R0: No residual tumor
- R1: Microscopic residual tumor
- R2: Macroscopic residual tumor

---

may be assumed to have residual tumor. Such patients may be classified as to whether the involvement is macroscopic or microscopic.

The pathology report should also indicate the presence of normal prostate tissue at the resection margin level. This might help the urologist explain why the serum PSA in patients with such a feature remains detectable after radical prostatectomy. In fact, the serum PSA value, even though very low, is not linked to tumor recurrence and persistence but to incomplete resection of the prostate gland.

Vascular invasion

By AJCC/UICC convention, vessel invasion (lymphatic or venous) does not affect the T category indicating local extent of tumor unless specifically included in the definition of a T category. In all other cases, lymphatic and venous invasion by tumor are coded separately. The TNM system uses the categories L and V to indicate the presence of lymphatic or venous invasion. Most of the time when vascular invasion is noted it is in tumors with fairly advanced pathology such that it is unclear as to its independent prognostic significance.[340]

Perineural invasion

Perineural invasion is one of the major mechanisms by which prostate cancer spreads out of the gland. Perineural invasion is almost ubiquitously present in radical prostatectomy specimens such that it is not useful as a prognostic parameter and we do not record it within radical prostatectomy pathology reports. As with all of the other parameters, the key question is whether the presence of (intraprostatic) perineural invasion in the prostatectomy specimen is an independent prognosticator. At this time it is not entirely clear whether there are differences in terms of prognosis between intraprostatic and extraprostatic perineural invasion.[151]

Volume of cancer

One of the most controversial aspects of the pathologic assessment of radical prostatectomy specimens is the measurement of tumor volume. The critical and controversial question concerns whether tumor volume is an independent prognostic parameter once other routinely assessed variables are accounted for.

There is one situation where it is important to give some estimate of tumor volume at radical prostatectomy. As a consequence of screening for prostate cancer, we have seen an increase in the resection of prostates harboring cancers that are so small that they are histologically difficult to identify. These cases currently account for approximately 4% of our radical prostatectomy specimens. The pathologist has to specify in the pathology report that these tumors

are 'small' or 'minute' (i.e., less than 0.5 cc) so that patients can be counseled that they are 100% cured of their tumor.

A consensus for a standard method of volume determination has not yet evolved. Volume is most precisely determined by stereologic methods, using either planimetry or point counting based on overlaid grids. However, the time and labor involved in these approaches will probably not lead to their wide acceptance. It has been recommended that at the very least, the proportion (percentage) of prostatic tissue involved by tumor be included for all specimens.[151]

Biomarkers to predict progression following radical prostatectomy

The drive to identify prognostic markers in prostate cancer is based on the perceived need to develop 'objective' markers to either supplant or supplement more 'subjective' markers that are currently in use (i.e., conventional histologic grading). The more established biomarkers are as follows: DNA ploidy, microvessel density (angiogenesis), Ki-67, neuroendocrine differentiation, p53, P27[kip1], p21[WAF1], bcl-2, Her-2/neu, E-cadherin, CD44, retinoblastoma (Rb) proteins, apoptotic index, androgen receptor status, PSA and PSAP expression, and nuclear morphometry[151] (Table 4.14).

It is important to recognize that these 'objective' markers are subject to the same variability as more conventional histologic parameters. One source of variability relates to different definitions of an abnormal result. There are also differences amongst studies in the methodology as to how to prepare and analyze the specimen for testing. There is also subjectivity in the interpretation of a test. There are also differences in terms of how the material is prepared prior to staining, which can affect results.

These newer techniques must be approached critically and rationally to determine whether they provide additional prognostic information beyond that which is currently available using more conventional parameters.[243,345]

Pelvic lymph node assessment

The adverse prognosis of metastatic disease to the pelvic lymph nodes is universally accepted. The incidence of pelvic lymph node metastases at the time of radical prostatectomy has decreased over the last couple of decades.[345,356] As a consequence of the declining incidence, concerns have been raised as to whether pelvic lymphadenectomy is necessary in all patients, especially those with a low risk of having positive lymph nodes based on pre-operative clinico-pathologic findings. The major factors contributing to this decrease are better patient selection as to who is a good candidate for surgery and the earlier detection of prostate cancer, both resulting from the use of serum PSA testing.

Intra-operative pathologic assessment of pelvic lymph nodes

The handling of lymphadenectomy specimens at the time of surgery is controversial and depends on the philosophy of the urologist. Some urologists will abort the radical prostatectomy in cases with positive lymph nodes identified at the time of surgery since surgery will not

Table 4.23 Reporting of regional lymph nodes

a. Number (specify location)
b. Number involved by tumor
    (1) Specify location, if possible
    (2) Size of metastatic deposit (i.e. if < 2 mm = micrometastasis)
    (3) Extracapsular extension, if present
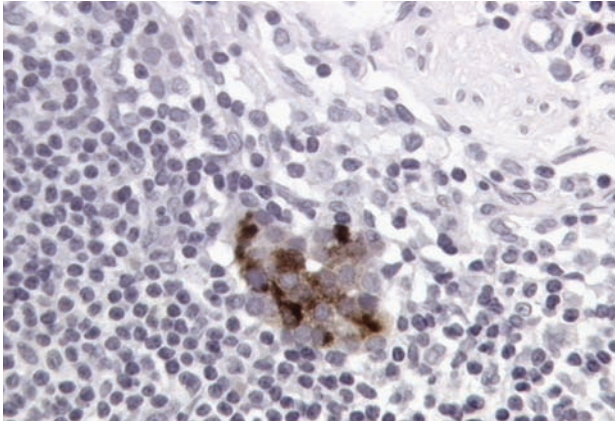
Figure 4.23
Isolated tumor cells are detected by immunohistochemistry.

Table 4.24 Regional lymph modes (pN0) and isolated tumor cells

■ pN0: No regional lymph node metastasis histologically, no examination for isolated tumor cells (ITCs)
■ pN0(i−): No regional lymph node metastasis histologically, negative morphologic (immunohistochemical) findings for ITCs
■ pN0(i+): No regional lymph node metastasis histologically, positive morphologic (immunohistochemical) findings for ITCs
■ pN0(mol−): No regional lymph node metastasis histologically, negative non-morphologic (molecular) findings for ITCs
■ pN0(mol+): No regional lymph node metastasis histologically, positive non-morphologic (molecular) findings for ITCs

be curative. With these urologists, the pathologist should try to optimize the identification of metastatic disease at the time of frozen section. Other urologists will proceed with radical prostatectomy when positive lymph nodes are found intra-operatively, as long as patients are projected to have a long survival and might benefit in terms of local control.

It is not practical to freeze all of the pelvic lymph nodes, especially given the low likelihood of finding metastatic disease even on permanent sections. A more reasonable approach would be to pre-operatively identify clinical parameters associated with such a low risk of lymph node metastases that frozen sections need not be performed.

Routine processing and reporting of pelvic node specimens

In 6.5% of the cases the only lymph node metastasis is not in a grossly recognized lymph node but in small lymph nodes embedded in the adipose tissue. Based on this, all of the adipose tissue from the pelvic lymphadenectomy specimens should be submitted for histologic examination. The detection of pelvic lymph node metastases may be enhanced through the use of special techniques. In particular, micrometastases can be immunohistochemically detected using antibodies to a keratin cocktail.

Table 4.23 reports the features that should be evaluated when examining lymph nodes.

Isolated tumor cells

Isolated tumor cells (ITCs) are single cells or small clusters of cells not more than 0.2 mm in greatest dimension. Lymph nodes or distant sites with ITCs found by either immunohistologic examination (Figure 4.23) or non-morphologic techniques (e.g., flow cytometry, DNA analysis, polymerase chain reaction (PCR) amplification of a specific tumor marker) should be classified as N0 or M0, respectively. Specific denotation of the assigned N category is suggested for cases in which ITCs are the only evidence of possible metastatic disease[357] (Table 4.24).

Table 4.25 Prognostic factors in localized prostate cancer

Prognostic factors	Tumor related	Host related	Environment related
Essential	Stage	Age	Socioeconomic factors
	Grade	Comorbidity	
	PSAlevel	Performance status	
Additional	Ploidy	Prior TURP	Access to care
		Race	Expertise
New and promising	PSMA		
	Kallikreins		
	Microvessel density		
	Mitotic figures		
	Cell adhesion		
	Neuroendocrine differentiation		
	EGFR		
	Androgen receptor		

*Denis L, Murphy GP. Prostate cancer. In: Gospodarowicz M, Henson DE, Hutter RVP, Eds. Prognostic Factors in Cancer, 2nd edn. Wiley-Liss 2001: Appendix 37B.1, 585.

Table 4.26 Prognostic factors in advanced prostate cancer*

Prognostic factors	Tumor related	Host related	Environment related
Essential	T,N,M categories Grade PSA level Pain	Age Comorbidity Performance status	Socioeconomic factors
Additional	Hemoglobin Alkaline phosphatase Creatinine		Access to care Expertise
New and promising	PSMA EGFR Androgen receptor		

*Denis L, Murphy GP. Prostate Cancer. In: Gospodarowicz M, et al eds. Prognostic Factors in Cancer, 2nd edn. Wiley-Liss 2001, Appendix 37B.2, 586.

UICC prognostic factor initiatives

In addition to the TNM project, the International Union Against Cancer (UICC) has supported a Prognostic Factor Project Committee which reviewed the literature on prognostic factors. The UICC has underscored the importance of prognostic factors in patient care, research, and also in cancer control programs. In the UICC prognostic factor system, essential, additional, and new and promising categories of prognostic factors are recognized. These clinical relevance based groupings are somewhat analogous to but not identical with the system proposed by the College of American Pathologists. The prognostic factors for localized and advanced prostate cancer taken from the 2001 monograph are shown in Tables 4.25 and 4.26.

Part 10

Inherited susceptibility, somatic gene defects, and androgen receptors

Inherited susceptibility

Currently, the evidence for a strong genetic basis in prostatic carcinoma is compelling: about 9% of all cases of PCa are thought to have a genetic basis, this is about twice the percentage of familial tumors seen in breast cancer. Strengthening the genetic evidence is a high frequency for PCa in monozygotic as compared to dizygotic twins in a large study of twins from Sweden, Denmark, and Finland[358] and the higher risk of developing PCa for men having other family members affected.[359]

The identification of highly penetrant PCa genes, i.e., genes that markedly increase the risk of cancer, has been particularly difficult for two main reasons. First, due to the advanced age of onset (median 60 years), availability of more than two generations to perform molecular studies on is difficult. Second, given the high frequency of PCa, it is likely that cases considered to be hereditary during segregation studies actually represent phenocopies, i.e., sporadic cases in families with high rates of PCa. In addition, hereditary prostate cancer (HPC) does not occur in any of the known cancer syndromes and does not have any clinical (other than a somewhat early age of onset at times) or pathologic characteristics to allow researchers to distinguish it from sporadic PCa.[360]

Hereditary PCa is characterized by Mendelian autosomal dominant or X-linked mode of inheritance, and an early onset of the disease. Based on the family clustering of PCa, a number of groups have worked to identify the genes involved. Generally, they have used linkage analysis of large families affected by PCa. Work over the past decade using genome wide scans in PCa families has identified high-risk loci.[2]

Susceptibility loci

There are at least seven susceptibility loci for PCa identified on different chromosomes.[5] Chromosome 1 is of particular interest, with three proposed loci. The chromosomal region 1q24–25, designated the locus of the hereditary prostate cancer (HPC1) gene, has been the most thoroughly investigated. Some analyses have confirmed a link between HPC1 and PCa, but others have failed to detect an association. The other two proposed susceptibility loci are 1q42.2–q43 (i.e., predisposing for PCa or PCaP) and 1p36 (i.e., cancer, prostate, and brain or CAPB). Additional loci have been identified on chromosome 16 (16q23.2), chromosome 17 (17p11, or HPC2, i.e., hereditary prostate cancer 2, also called ELAC2), chromosome 20 (20q13 or HPC20), and chromosome X (Xq27–28 or HPCX). The candidate HPC genes in these regions have rarely been identified, although potential predisposing genes for HCP1 and HCP2 regions have now been cloned.[2]

Candidate HPC genes

Mutations in a growing number of candidate HPC loci and genes have been detected, suggesting that defects in critical pathways involving DNA damage response, apoptosis, and innate immunity may have a particular important role in the initiation of PCa. The types of alterations associated with such genes are basically represented by base substitutions, deletions, and insertions.[2] The following highly penetrant genes probably account for 10% or less of hereditary PCa cases:[3] *RNASEL* (a candidate tumor suppressor gene within the HPC1 locus located on 1q24–25),[361,362] *MSR1* (located on 8p22, encodes subunits of class A macrophage-scavenger receptor 1),[363] *CYP17* (located on 10q24.3, encodes cytochrome P-450c17α, an enzyme that catalyzes key reactions in sex-steroid biosynthesis),[364] *HPC2/ELAC2* (located on 17p11 and is considered a tumor suppressor gene),[365] *BRCA2* (located on chromosome 13q),[365] and *CHEK2* (encodes an upstream regulator of p53 in the DNA damage signaling pathway).[366] A number of germline variants and mutations of these genes have been associated with increased risk of PCa.

An increased risk of PCa has been associated with sexually transmitted infections, regardless of the pathogen, suggesting that inflammation, rather than infection, initiates prostatic carcinogenesis. Inflammatory cells elaborate numerous microbiologic oxidants than might cause cellular or genomic damage in the prostate.[3] Two of the candidate PCa susceptibility genes identified thus far, *RNASEL* and *MSR1*, encode proteins with critical functions in host response to infections. Mutations in these genes might reduce the ability to eradicate infectious agents, thus resulting in chronic inflammation. *RNASEL* is believed to regulate cellular proliferation and apoptosis through the interferon-inducible 2′,5′-oligoadenylate-dependent RNA decay pathway. At least two mutations inactivating *RNASEL* have been identified that are potentially responsible for PCa cases in families showing linkage to HPC1.[361,362] Germline *MSR1* mutations have been linked to PCa in some families with early-onset hereditary PCa.[363,367]

BRCA2, located on chromosome 13q, is a gene that has been implicated as a prostate cancer susceptibility locus primarily due to its analysis in breast cancer families. Studies of families with breast cancer suggest that male carriers of *BRCA2* mutations are at increased risk for PCa, particularly at an early age. Inactivating mutations in *BRCA2* have been reported in approximately 2% of men with early onset PCa, conforming the relevance of this gene to PCa susceptibility.[365,367]

Genetic polymorphisms

Perhaps even more important in terms of inherited susceptibility for PCa are common polymorphisms in a number of low penetrance alleles of other genes – the so-called genetic modifier alleles. The major

pathways currently under examination include those involved in androgen action, DNA repair, carcinogen metabolism, and inflammation pathways.[2,368] It is widely assumed that the specific combinations of these variants, in the proper environmental setting, can profoundly affect the risk of developing PCa.

The androgen receptor (AR) gene, a member of the steroid and thyroid hormone receptor gene superfamily, is a transcription factor that mediates the action of androgen in prostate cells. It is located on Xq11–12. The amino-terminal domain encoded by exon 1 contains a variable number of trinucleotide repeats.[368] Decreased transactivation activity and binding affinity for androgen is associated with an increased number of trinucleotide repeats. Shorter CAG repeat lengths have been associated with a greater risk of developing PCa.[369–372]

Additional examples of genetic polymorphisms are related to *SRD5A2* – a gene located on 2p23 that encodes a polypeptide that catalyzes the conversion of testosterone to dihydrotestosterone – and to vitamin D receptor (VDR). Polymorphisms in the former have been reported to confer an increased risk of PCa, particularly in African Americans and Hispanics.[373] The contribution of the VDR gene polymorphisms to PCa susceptibility remains controversial.[374]

Somatic gene alterations

Many somatic mutations, gene deletions, gene amplifications, chromosomal rearrangements, and changes in DNA methylation are detectable in PCa cells at the time of diagnosis. These alterations probably accumulate over a period of several decades and the number of changes increases with the stage of the disease. Telomerase activity is frequently upregulated in PCa. This may contribute to genetic instability and promote neoplastic transformation.[375–377] Although multiple alterations that appear to contribute to disease progression have been suggested, no single key change has been detected.[378,379]

Gene alterations

Table 4.27 summarizes the most common somatic gene alterations in PCa. The role of *PTEN*, *CDKN1B*, and *AMACR* has been investigated in several recent publications.

PTEN (phosphatase and tensin homolog) is a tumor-suppressor gene encoding a phosphatase active against both protein and lipid substrates. *PTEN* induces G1 cell cycle arrest via negative regulation of the phosphatidylinositol 3′-kinase/protein kinase B (PI3/Akt) signaling pathway that is essential for cell-cycle progression and cell survival. By inhibiting PI3K/Akt, *PTEN* can increase the levels of *CDKN1B* messenger RNA and p27 protein (see below). *PTEN* is frequently mutated or deleted in PCa cell lines and tumors. *PTEN* alterations are more common in metastatic deposits than in primary carcinomas. By immunohistochemistry, PTEN is present in normal epithelial cells and PIN. The level of PTEN is frequently reduced in PCa of high grade or stage. Somatic allelic losses (i.e., haploinsufficiency) in both *PTEN* and *NKX3.1* appear to be common in prostate carcinoma and may promote an abnormal proliferation of prostate cells.[380–382]

CDKN1B encodes p27^{kip1}, a cyclin-dependent kinase inhibitor. The p27^{kip1} protein regulates cell-cycle progression from G1 to S phase by its inhibitory interaction with the cyclin E/cdk2 complex. In PCa, p27^{kip1} expression progressively decreases with increasing tumor grade and stage. Low levels of p27^{kip1} may be as much a result of *CDKN1B* alterations as of the PTEN loss whose function is mediated by the PI3K-Akt signaling pathway.[383–385] A paper by Dreher et al dealt with a combined analysis of PTEN and p27^{kip1} expression in PCa and greatly contributed to the knowledge that activated Akt blocks p27^{kip1} entry into the nucleus by phosphorylating a residue within the nuclear localization signal of p27^{kip1}.[386]

AMACR (alpha-methylacyl-CoA racemase) encodes an enzyme that plays an important role in the β-oxidation of branched-chain fatty acids and serves as a 'caretaker' gene. It has been found consistently upregulated in PCa and high-grade prostatic intraepithelial neoplasia (HGPIN), a direct precursor of PCa.[360,387–390]

DNA methylation

Epigenetic events that can affect gene expression without altering the actual sequence of DNA include phenomena such as DNA methylation, chromatin remodeling, histone modification, and RNA interference.[2] Many gene promoters are associated with GC rich regions of the DNA known as CpG islands. Abnormal methylation

Table 4.27 Somatic gene alterations in PCa

Gene	Location	Alteration
AMACR (alpha-methylacyl-CoA racemase)	5p13.2	Increased expression
EZH2 (enhancer of zeste homolog 2)	7q35	Increased expression
NKX3.1 (NK3 transcription factor homolog A)	8p21	Decreased expression
KLF-6 (Kruppel-like factor 6)	10p15	Decreased expression
PTEN (phosphatase and tensin homolog)	10q23.3	Decreased expression
KAI1	11p11.2	Decreased expression
CDKN1B (cyclin-dependent kinase inhibitor)	12p12	Decreased expression
RB (Retinoblastoma susceptibility gene)	13q	Decreased expression
Hepsin	19q11–13.2	Increased expression

of CpG islands located within gene promoters is associated with decreased transcriptional activity and it occurs in many types of cancers. Abnormal methylation of genes such as those involved with control of cellular growth or detoxification is believed to have a critical role in early stages of PCa progression.[3] A certain number of genes, such as *GSTP1* and *E-cadherin*, are commonly methylated in human PCa.

GSTP1 (pi-class of glutathione S-transferase), located on 11q13, probably serves as a caretaker gene. It defends prostate cells against genomic damage mediated by carcinogens or various oxidants. *GSTP1* demonstrates hypermethylation in more than 90% of prostate carcinomas, thus preventing expression of this protective gene.[360,391–393]

E-Cadherin, located on 16q22.1, encodes a Ca^{2+}-dependent cell adhesion molecule that is important in normal cell growth and development and is considered a suppressor of neoplastic invasion. E-Cadherin is methylated in approximately 50% of cases.[4] Decreased expression of E-cadherin has been detected in several primary and metastatic prostate carcinomas.[394,395]

Androgen receptors

Many somatic alterations of androgen receptors (ARs) have been detected in those PCas that progress despite hormonal treatment.[368] At the same time, prostate tumor cells appear to have several possible mechanisms by which they could become androgen refractory (a comprehensive review of these mechanisms is given in reference 396).[397]

Mutations in the AR hormone-binding domain or amplification of the AR gene could increase tumor cell sensitivity to androgens. In fact, the increased levels of AR DNA are associated with an increase in AR messenger RNA. Increased levels of AR protein associated with AR gene amplification have been implicated in the ability of cells to more effectively use the low levels of androgens that are produced by the adrenal glands and that are still available during androgen deprivation therapy.[398]

Mutations of the AR could allow it to respond to other steroids or even to anti-androgens. In particular, mutations in the ligand-binding domain of AR could not only increase sensitivity to normal ligands, such as adrenal androgens, which are present at low levels, but also may cause the AR to be responsive to other molecules, such as antiandrogens, which are not normal ligands.[399]

Alterations of the interactions between the AR and some of its coactivators could allow unmutated and mutated AR to become activated by adrenal androgens, other steroids, or anti-androgens. There are several possible ways by which co-activators may be involved in the progression of androgen-sensitive PCa to androgen-refractory PCa. First, overexpression of certain co-activators may cause activation of ARs by non-androgenic steroids. Second, overexpression of other co-activators may cause activation of ARs by anti-androgens. Third, AR mutations may result in conformational changes of the AR that, in combination with certain co-activators, can result in activation of the AR. These three mechanisms, alone or in combination, may provide a means for PCa cells to overcome their initial dependence on androgens.[368]

Alterations in the expression or function of genes in regulatory pathways involving peptide growth factors or cytokines could cause inappropriate activation of the AR. For instance, growth factors serve as ligands for receptor tyrosine kinases and activate downstream intracellular kinase cascades. Receptor tyrosine kinases may also be involved in the progression to androgen-refractory PCa through an interaction with the AR. The receptor tyrosine kinase Her2/Neu (also known as erbB2) is expressed at low levels in normal epithelial cells. Several studies have demonstrated Her2/Neu protein overexpression and/or gene amplification in a subset of PCa patients. Overexpression of Her2/Neu not only stimulates proliferation of LNCaP cells but also enhances AR-transactivating activity, both in the absence and presence of androgens, in which case activation is synergistic. Moreover, Her2/Neu induces PSA expression, and this induction can be partially inhibited by blocking the MAP kinase pathway. Thus, MAP kinase may mediate the activation of the AR by Her2/Neu.[400]

The AR could be bypassed entirely, possibly as a result of constitutive activation of regulatory molecules downstream of the AR. For instance, PTEN inactivation, p53 mutations, bcl-2 pathway alterations, neurondocrine factors, and alternative growth factor regulation and utilization could bypass the need for activation of the AR.[401]

Part 11

Rare forms of tumors

Basal cell carcinoma of the prostate and basal cell hyperplasia

Basal cell proliferations in the prostate gland exhibit a morphologic continuum ranging from basal cell hyperplasia in the setting of nodular hyperplasia to malignant basal cell lesions that resemble, to a certain degree, basal cell carcinoma of the skin and adenoid cystic carcinoma of the salivary gland.[402,403] A large number of terms have been used for these neoplasms and related growths.

Morphology

A spectrum of basal cell proliferations ranging from hyperplasia to carcinoma exists in the prostate[404] (Table 4.28). These are usually located in the transition zone.

Ordinary (usual, typical, or classical) basal cell hyperplasia (BCH) (Figure 4.24(A)) consists of numerous small to normal-sized, round basophilic acini with several layers of basal cells (glandular architectural type) or solid nests either arranged in a lobular configuration or rarely 'infiltrating' the stroma (see below). The morphology corresponds to our pattern 1. None of the cases of ordinary BCH, by definition, contains either prominent nucleoli (their mean diameter is less than 1 μm)[402] or polymorphism; however, rare cases may show the presence of hyperchromatic nuclei, enlarged nuclei, and rare mitotic figures. BCH resembles prostate acini seen in the fetus, accounting for the synonyms 'fetalization' and 'embryonal hyperplasia'. BCH may be composed of basal cell nests with areas of luminal differentiation resembling similar lesions of the salivary gland. This is denoted as the adenoid basal form of BCH.

Basal cell adenoma is identical to ordinary BCH, although the proliferating basal cell masses are usually large and circumscribed, with nodular or adenoma-like pattern. In contrast to basal cell carcinoma, basal cell adenoma is well circumscribed, lacks necrosis, and the stroma between the basal cell nests is similar to that of the surrounding normal prostatic stroma. Occasionally, BCH is multifocal (*adenomatosis*). The terms basal cell adenoma and adenomatosis are very rarely used.

Four morphologic findings of BCH have been reviewed:[405] intracytoplasmic globules (these stain for alpha-fetoprotein and

Table 4.28 Basal cell proliferations of the prostate

- Ordinary (usual) basal cell hyperplasia (including basal cell adenoma and adenomatosis)
- Florid basal cell hyperplasia
- Basal cell hyperplasia with prominent nucleoli (or atypical basal cell hyperplasia)
- Basal cell carcinoma (adenoid cystic carcinoma)
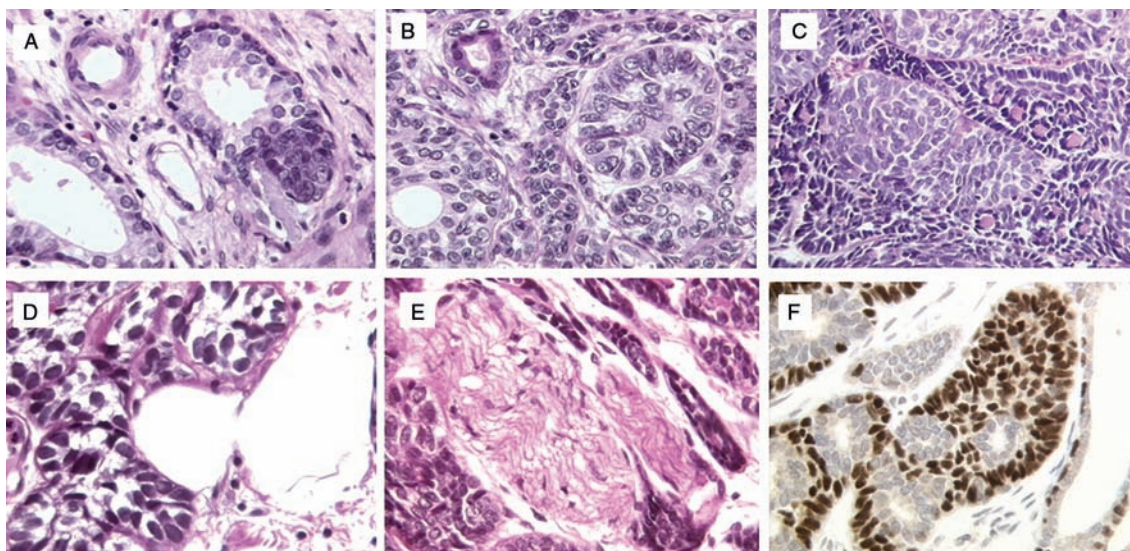
Figure 4.24
Basal cell carcinoma of the prostate and basal cell hyperplasia. (A) Ordinary (usual, typical, or classical) basal cell hyperplasia. (B) Florid basal cell hyperplasia. (C) Basal cell carcinoma. (D) Extension out of the prostate. (E) Perineural invasion. (F) The proliferating cells are p63 positive.

alpha-1 antitrypsin), calcifications, squamous features, and cribriform. Recognition of intracytoplasmic globules can help to identify a lesion as that of BCH. This feature, reported also by Yang et al,[406] has not been seen in other prostatic lesions. Intraluminal calcifications can also aid in the recognition of BCH, given their rarity in other prostatic conditions. Knowledge that squamous and cribriform findings of BCH exist and awareness of their light microscopic and immunohistochemical features can help to distinguish these lesions from preneoplastic and neoplastic diseases of the prostate.

BCH may have a florid appearance (i.e., *florid basal cell hyperplasia*) (Figure 4.24(B)). Our pattern 2 is identical to this and corresponds to the description given by Van de Voorde et al:[407] compact glandular proliferation with solid nests; the cytology in some areas looks disturbing because the cells have a moderately enlarged nucleus, often with a prominent nucleolus; a few mitotic figures are present; the intervening stroma is scant and cellular; the lesions are not well circumscribed and are intermingled with the surrounding glands, giving the impression of 'infiltration' (this is also called diffuse type). Yang et al gave an additional criterion for the identification of florid BCH: extensive proliferation of basal cells involving more than 100 small crowded acini (per section) forming a nodule.[406]

BCH may have prominent nucleoli (i.e., *basal cell hyperplasia with prominent nucleoli*), but is otherwise identical to ordinary BCH. The nucleoli are round to oval and lightly eosinophilic, similar to those seen in acinar adenocarcinoma of the prostate (their mean diameter is 1.96 μm). There is chronic inflammation in most cases, suggesting that nucleolomegaly is a reflection of reactive atypia.[402] These cases are also referred to as *atypical basal cell hyperplasia*.[402,403]

BCH with prominent nucleoli may be mistaken for HGPIN (Table 4.29). Although occasionally the distinction between these two entities may be difficult, usually they are distinct. The nuclei in BCH tend to be round whereas, at times, the cells form small solid basal cell nests. In contrast, the cells in PIN tend to be more pseudostratified and columnar and do not occlude the glandular lumina. Within areas of BCH, atypical looking basal cells can be seen under the overlying benign-appearing secretory cells. PIN has full-thickness cytologic atypia with the nuclei oriented perpendicular to the basement membrane. The use of antibody against either 34betaE12 or p63 can help in difficult cases. In BCH immunohistochemistry shows multilayered staining of the basal cells, whereas an interrupted immunoreactive basal cell layer is seen in PIN. Yang et al[408] showed that immunostaining for alpha-methylacyl-coenzyme racemase (i.e., P504S) is negative in florid BCH and positive in HGPIN and adenocarcinoma. Immunostaining for glutathione-S-transferase pi (GST-pi) is positive in florid BCH and negative in adenocarcinoma. The same group of authors performed ultrastructural analysis to further document the basal cell features of florid BCH.

BCH, mainly with a glandular architecture or when florid, may be confused with adenocarcinoma. BCH can be distinguished from adenocarcinoma by its very basal cell appearance. The glands appear basophilic at low power due to multilayering of basal cells which have scant cytoplasm. In contrast, gland-forming adenocarcinoma of the prostate almost always has more abundant cytoplasm, resulting in a more eosinophilic appearance to the glands. If by light microscopy there is difficulty in distinguishing BCH from prostatic adenocarcinoma, utilization of immunohistochemistry with basal cell specific antibodies (34betaE12 or p63) can differentiate between these two lesions.[409]

Basal cell carcinoma (basal cell carcinoma/adenoid cystic carcinoma) (Figure 4.24(C)) is characterized by proliferation of cells arranged in various architectural patterns. Two morphologic variants of basal cell carcinomas can be recognized in the prostate. Islands and cords of epithelial cells with peripheral palisading characterize the first type, morphologically similar to basal cell carcinoma of the skin. The second type, also called adenoid cystic carcinoma, is composed of nests of infiltrating tumor cells with an adenoid cystic pattern, morphologically similar to the adenoid cystic carcinoma of the salivary glands. The case presented here, with its pattern 3, belongs to the first variant, even though few areas with the second are observed. Focal squamous differentiation and clear cell appearance are seen.

The diagnostic criteria for malignancy in basal cell carcinoma include: (a) extensive infiltration between normal prostate glands, (b) extension out of the prostate, (c) perineural invasion, or (d) necrosis[402,403,410] (Table 4.30). The most obvious criterion of malignancy observed in the current case was the extension out of the prostate (Figure 4.24(D)). Perineural invasion was also seen (Figure 4.24(E)). Our case showed the presence of focal areas of basal cell carcinoma mimicking the classical BCH.

The differential diagnosis of basal cell carcinoma includes poorly differentiated (mostly Gleason's grade 5) adenocarcinoma (basal cell carcinoma may occur, rarely, in combination with conventional adenocarcinoma) and urothelial carcinoma (Table 4.31). Poorly differentiated adenocarcinoma may grow in solid nests and, similarly to basal cell carcinoma, is not reactive for PSA. Lack of immunoreactivity for p63 and 34betaE12, however, is helpful in recognizing conventional adenocarcinoma, though it has been reported that this tumor may occasionally express p63. Similarly to basal cell carcinoma, urothelial carcinoma may exhibit a solid growth pattern with peripheral palisading and central necrosis and may express high levels of p63. However, urothelial carcinoma

---

Table 4.30 Basal cell carcinoma: diagnostic criteria for malignancy

- Extensive infiltration between normal prostate glands
- Extension out of the prostate
- Perineural invasion
- Necrosis

Table 4.29 Basal cell hyperplasia (ordinary, florid, and with nucleoli): differential diagnoses

- High-grade PIN
- Acinar adenocarcinoma
- Sclerosing adenosis
- Benign seminal vesicle/ejaculatory duct epithelium
- Squamous metaplasia
- Transitional cell metaplasia

Table 4.31 Basal cell carcinoma: differential diagnoses

- Poorly differentiated adenocarcinoma (mostly Gleason's grade 5)
- Transitional cell (urothelial) carcinoma
- Neuroendocrine carcinoma
- Basaloid carcinoma of the rectum

expresses CK20 and CK7. Basal cell carcinoma is positive for CK7 and negative for CK20.[411]

Immunohistochemistry

The results of the immunohistochemical investigations published by different groups have pointed out the following four features.

The first is related to the nature of the cells involved in the basal cell proliferations. Immunohistochemistry clearly indicates that they have the same immuno-phenotype of the basal cells present in normal ducts and acini. The cells are positively and strongly stained with 34betaE12 and p63 (Figure 4.24(F)). These are the two consolidated markers for the basal cells in the prostate, as seen also in our case, and their absence is in favor of prostate adenocarcinoma.[409]

The second concerns cell composition. Our investigation points out that there might be at least three types of cells: (a) cells with a palisading aspect in close contact with the stroma, (b) cells in the center of the nests where lumina are seldom seen, and (c) cells in between these two types. McEntee et al were the first to document the heterogeneous cell composition in prostatic BCH and neoplasia in their comparative pathology study in human and non-human primates.[412]

The cells in contact with the stroma show focal positivity for S-100 and alpha-smooth muscle actin. The expression of these two markers indicates that myo-epithelial differentiation appears in the basal cell proliferations, as usually takes places in sclerosing adenosis, whereas it is absent in normal prostate. This type of differentiation was mentioned both in benign and malignant basal cell lesions in at least two previous publications.[406,407] The exact location of the myo-epithelial cells was documented by Yang et al.[408] Grignon et al observed the presence of S-100 positivity in the absence of reactivity with muscle-specific actin.[413] They concluded that S-100 positivity alone does not necessarily indicate myo-epithelial cell differentiation.

The cells that are located in the center of the nests and those lining the small lumina stain positively with AE1/AE3, whereas the cells in the other two locations are negative. The same cells are 34betaE12 and p63 negative[403] and only rarely express a faint positivity for PSA. The basal cells in the normal ducts and acini do not stain with AE1/AE3, whereas all the cells present in ducts and acini with atrophic features are intensely stained. Such findings indicate that the cells present in the basal cell proliferations show some degree of differentiation towards the secretory cell phenotype.

Mitoses and Ki-67 positivity are mainly seen in the nuclei that in the nests occupy an intermediate spatial position between the peripherally and centrally located cells. This indicates that the cells in such locations belong to a kind of proliferative compartment, whereas the cells in contact with the stroma and those in the center represent the differentiative/differentiated compartment.[407]

The third interesting feature is that the basal cell proliferations express two markers usually seen in neoplasias of other sites and organs. The first is the demonstration of laminin both in the stroma surrounding the cell nests and in small eosinophilic globules surrounded by the cells. This feature is usually seen in tumors of the salivary glands. The other is represented by the expression of c-erbB-2 onco-protein, similar to that seen in breast cancer.

The fourth is represented by the presence of a small proportion of cells with neuroendocrine differentiation, as documented by chromogranin immunostaining.[406]

Differential diagnosis between basal cell hyperplasia and basal cell carcinoma

In contrast with BCH, basal cell carcinoma appears infiltrative rather than lobulated, with invasion around nerves, or into soft tissues, and with necrosis. Proliferation (assessed by Ki-67 immunostaining) is also helpful in distinguishing basal cell carcinoma from the other basal cell proliferations. The proliferation index in basal cell carcinoma is greater than in the ordinary BCH, the values in florid BCH and BCH with prominent nucleoli being intermediate between ordinary BCH and basal cell carcinoma.[406] Proliferation in areas of basal cell carcinoma with the pattern mimicking BCH is as high as in the classical nested type of basal cell carcinoma.[407]

Morphology and immunohistochemistry suggest that florid BCH has an intermediate position between ordinary BCH and basal cell carcinoma. The exact position of BCH with nucleoli is not entirely clear. There is a lack of clinical information in the very few studies with the follow-up of the patients. However, it shows morphologic features of both ordinary and florid BCH.

Relationship between basal cell hyperplasia and basal cell carcinoma

The clinical presentation and history of the case included in this investigation gives support to the view expressed by Reed,[414] according to which BCH is a preneoplastic lesion. In particular, florid BCH could derive from ordinary BCH and could be the direct precursor of basal cell carcinoma. This view is also supported by the observation made by some authors on the occurrence of extensive BCH in the prostate with basal cell carcinoma.[402,403,411,413,415]

Natural history of basal cell carcinoma

The English literature on this entity consists of only a few publications.[416] (For an extensive list of previously published cases see references 410 and 411.) Patients are generally elderly, presenting with urinary obstruction, TURP being the most common tissue source of diagnosis. The youngest reported case was 28 years old.[415] The outcome for patients diagnosed with basal cell carcinoma of the prostate is uncertain, since most cases have been reported with a short follow-up. Overall, basal cell carcinoma of the prostate is viewed as a low-grade carcinoma.[410] A paper by Iczkowski et al[417] described the clinico-pathologic features in 19 cases and, based on their experience, they concluded that basal cell carcinoma of the prostate (in their paper this tumor is referred to as adenoid cystic/basal cell carcinoma) was a potentially aggressive neoplasm requiring ablative therapy. Such conclusion was based on the fact that metastasis was documented in 21% of their cases, while two died of cancer and three were alive with cancer.

Urothelial carcinoma of the prostate

The frequency of primary urothelial carcinoma ranges from 0.7 to 2.8% of prostatic tumors in adults.[418,419] In patients with invasive bladder carcinoma, there is involvement of the prostate gland in up to 45% of cases.[420–422] Primary urothelial carcinoma is usually located within the proximal prostatic ducts. Many cases are locally advanced at diagnosis and replace the prostate gland (Figure 4.25). Primary urothelial carcinoma presents in a similar fashion to other prostatic masses including urinary obstruction and hematuria.[419] Digital rectal examination is abnormal in the majority, but is infrequently the presenting sign.[423] There are limited data on PSA levels in patients with urothelial carcinoma of the prostate.

Most cases are diagnosed by transurethral resection or less often needle biopsy.[423] In all suspected cases the possibility of secondary involvement from a bladder primary must be excluded; the bladder tumor can be occult and random biopsies may be necessary to exclude this possibility.[424,425]

Tumor spread and staging

In situ carcinoma can spread along ducts and involve acini or, similar to bladder carcinoma in situ, tumor can spread along ejaculatory ducts and into seminal vesicles. Initial spread is by invasion of prostatic stroma. Local spread beyond the confines of the prostate may occur. Metastases are to regional lymph nodes and bone.[426] Bone metastases are osteolytic. These tumors are staged as urethral tumors.[427] For tumors involving the prostatic ducts, there is a T1 category for invasion of subepithelial connective tissue distinct from invasion of prostatic stroma (T2). The prognostic importance of these categories has been confirmed in clinical studies.[428] The full range of histologic types and grades of urothelial neoplasia can be seen in primary and secondary urothelial neoplasms of the prostate.[428]

Prognosis

For patients with either primary or secondary urothelial carcinoma of the prostate the single most important prognostic parameter is the
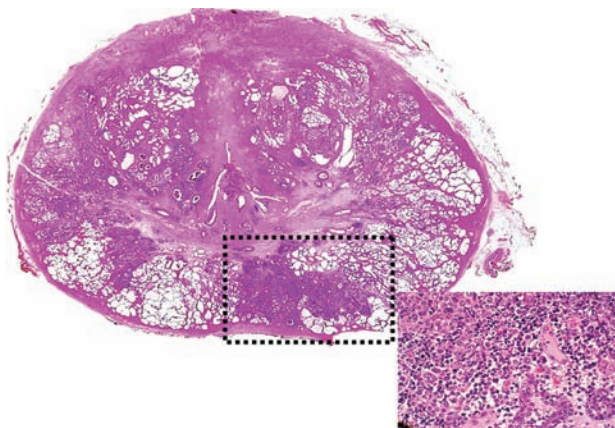
Figure 4.25
Urothelial carcinoma of the prostate (dotted area). The insert shows the histologic features of this tumor.

presence of prostatic stromal invasion. With stromal invasion or extension beyond the confines of the prostate prognosis is poor.[419,428–430]

Squamous cell neoplasms of the prostate

Squamous cell carcinomas may originate either in the periurethral glands or in the prostatic glandular acini, probably from the lining basal cells which show a divergent differentiation pathway.[431,432] Approximately 50% of adenosquamous carcinomas may arise in prostate cancer patients subsequent to endocrine therapy or radiotherapy.[433] The incidence of squamous cell carcinoma of the prostate is less than 0.6% of all prostate cancers.[434,435] Even more rare is adenosquamous carcinoma of the prostate.

Clinical features

Most, if not all pure squamous cell carcinomas become clinically manifest by local symptoms such as urinary outflow obstruction, occasionally in association with bone pain and hematuria. Adenosquamous carcinomas may be detected by increased serum PSA, but more typically by obstruction of the urinary outflow, requiring transurethral resection.[433] A proportion of cases show an initial response to hormone therapy.[436,437]

Histopathology

By definition pure squamous cell carcinomas do not contain glandular features and they are identical to squamous cell carcinomas of other organs (Figure 4.25). Primary prostatic squamous cell carcinomas must be distinguished on clinical grounds from secondary involvement of the gland by bladder or urethral squamous carcinomas. Histologically, squamous cell carcinoma must be distinguished from squamous metaplasia as may occur in infarction or after hormonal therapy.

Adenosquamous carcinomas are defined by the presence of both glandular (acinar) and squamous carcinoma components. The glandular tumor component generally expresses PSA and PAP, whereas the squamous component displays high-molecular-weight cytokeratins.[433]

Prognosis

Both squamous cell carcinomas and adenosquamous carcinomas tend to metastasize rapidly with a predilection for the skeletal bones.[435,438]

Adenocarcinoma arising from the prostatic urethra

Even more rare are cases of in situ and infiltrating mucinous adenocarcinoma arising from glandular metaplasia of the prostatic urethra with invasion into the prostate.[439] The histologic growth patterns

found in these tumors were identical to mucinous adenocarcinoma of the bladder consisting of lakes of mucin lined by tall columnar epithelium with goblet cells showing varying degrees of nuclear atypia and, in some of these cases, mucin-containing signet cells. These tumors have been negative immunohistochemically for PSA and PAP.

Neuroendocrine tumors of the prostate

Neuroendocrine differentiation in prostatic carcinoma has three forms:

1. focal neuroendocrine differentiation in conventional prostatic adenocarcinoma;
2. carcinoid tumor (WHO well-differentiated neuroendocrine tumor); and
3. small cell neuroendocrine carcinoma (new WHO classification poorly differentiated neuroendocrine carcinoma).

True carcinoid tumors of the prostate are exceedingly rare.[177,440,441] These tumors show classic cytologic features of carcinoid tumor seen elsewhere. The prognosis is uncertain due to the small number reported.

The term 'carcinoid-like tumors' has been used to refer to a variety of miscellaneous entities, most of which refer to ordinary acinar carcinoma of the prostate with an organoid appearance and focal neuroendocrine immunoreactivity.

Part 12

Non-epithelial tumor-like conditions and tumors of the prostate stroma

A wide variety of soft tissue lesions occur in the prostate, including reactive stromal proliferations, benign neoplasms, and sarcomas (Table 4.32). Although many of these tumors are distinguished easily, considerable diagnostic difficulty may be encountered with some of the rare and newly identified lesions. Patient age and clinical history are essential in this setting. The serum PSA concentration is usually not significantly elevated.

Atypical spindle cell lesions of the prostate

Many of the prostatic non-epithelial tumor-like conditions and tumors show a spindle cell appearance.[442] The most common lesion is represented by benign stromal prostatic hyperplasia, which is easy to recognize because of the usual association with areas of glandular proliferation.

Several cases of benign lesions with a spindle cell pattern have been reported, primarily in the urinary bladder, but also in the prostate.[443] In certain instances, these lesions mimicked and were interpreted as sarcomas, and the patients were treated aggressively.[444]

Table 4.32 Classification of prostatic non-epithelial tumor-like conditions and tumors

Tumor-like proliferations and inflammatory pseudotumors
- Postoperative spindle cell nodules
- Inflammatory myofibroblastic tumor
- Blue nevus
- Granulomatous prostatitis

Variants of prostatic hyperplasia
- Stromal hyperplasia with atypia
- Fibroadenoma-like foci in benign hyperplasia
- Phyllodes-like hyperplasia

Cystoadenoma

Mixed epithelial–stromal tumor (phyllodes tumor)

Stromal tumors
Benign
- Leiomyoma, including its variants (atypical leiomyoma, cellular leiomyoma, and leiomyoblastoma)
- Others
Malignant
- Rhabdomyosarcoma
- Leiomyosarcoma
- Stromal sarcoma
- Others

Sarcomas in the prostate are rarely reported and represent merely 0.1% of prostatic malignant neoplasms.[445] The most common sarcomas are rhabdomyosarcoma and leiomyosarcoma. The former is more common in children and bears a very poor prognosis, whereas the latter follows a slower course, but generally recurs after initial therapy.[446]

Because of the greater differences in clinical behavior and management associated with these two groups of lesions, distinctive morphologic features were sought. However, determining such features is further complicated by the extreme rarity of both benign spindle cell lesions and sarcomas.

Pseudomalignant (or pseudosarcomatous) spindle cell proliferations

Reactive, non-neoplastic fibrous lesions of soft tissue that, because of their clinical presentation, gross appearance, growth pattern, and light microscopic features, may be mistaken for a malignancy, usually a sarcoma, are often referred to as pseudosarcomas. These lesions can be divided into two groups distinguished by differences in etiology and morphologic appearance, e.g., postoperative spindle cell nodule and inflammatory pseudotumor.[442]

A clear morphologic distinction between postoperative and spontaneous spindle cell lesions cannot be easily made in all instances. Therefore, the designation of 'pseudomalignant spindle cell proliferations' has been suggested as a blanket term for all types of non-neoplastic spindle cell proliferations, independently of etiology. The use of the term 'pseudomalignant' is considered useful to stress the benign nature of the lesions and frequent similarities they may have to various types of spindle cell malignancy.

Postoperative spindle cell nodule, also called postsurgical inflammatory myofibroblastic tumor, is a rare benign reparative process occurring within a few months of surgery and consists of nodules of spindle cells arranged in fascicles with a variable number of mitotic figures. The cells have abundant cytoplasm; the nucleus is centrally located and elongated to ovoid in shape; small prominent nucleoli are present. The features that can be used to distinguish a postoperative spindle cell nodule from a sarcoma are:

- lack of significant nuclear pleomorphism and of atypical mitoses
- plexiform pattern of blood vessels
- presence of chronic inflammation
- small size of the nodule
- lack of recurrence after conservative excision.

Inflammatory pseudotumor, also called postoperative spindle cell nodule with no prior operation, is a rare benign pathologic entity of unknown etiology occurring in the prostate, urethra, bladder and
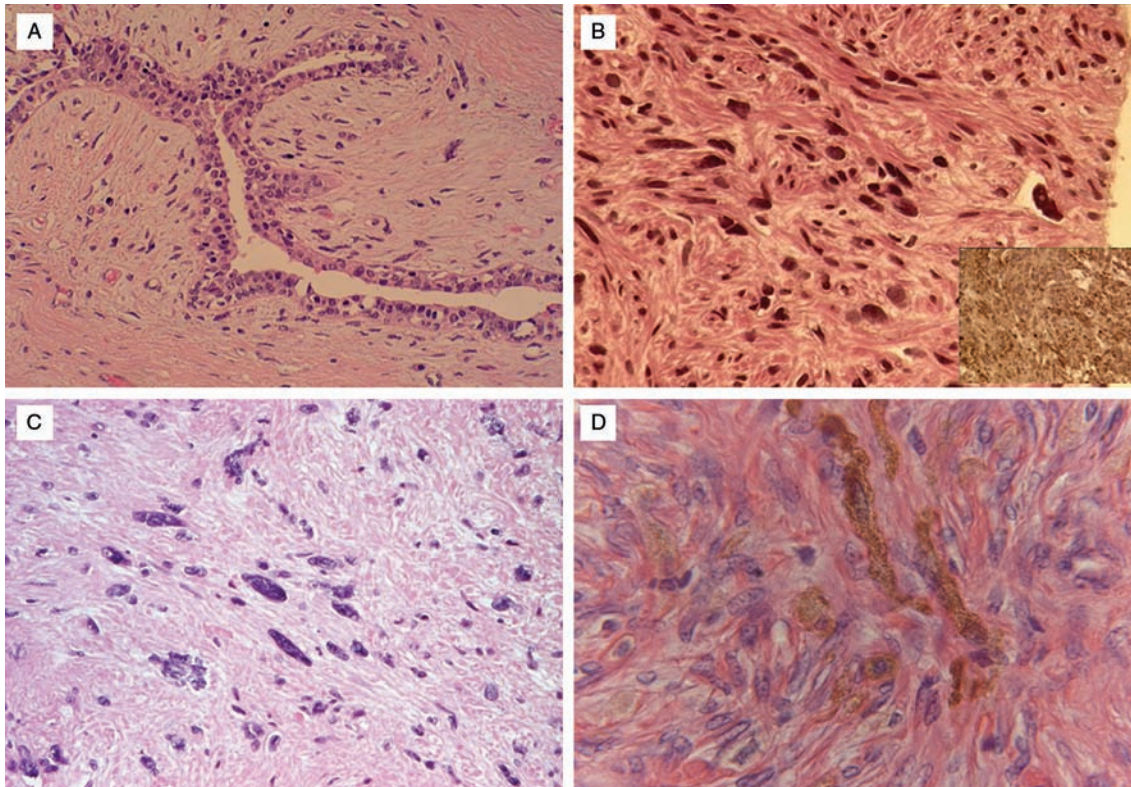
Figure 4.26
(A) Benign phyllodes tumor. (B) Leiomyosarcoma (insert: the tumor is smooth muscle actin positive). (C) Atypical leiomyoma.
(D) Prostatic blue nevus.

other sites without a history of prior surgery. Histologically, this lesion resembles granulation tissue with variable cellularity. Cells are more haphazard in their distribution than postoperative spindle cell nodules. Lesions often show a densely cellular spindle cell pattern admixed with a very myxoid component. Cells resemble those seen in nodular fasciitis with a tissue culture appearance. Occasionally there may be prominent nucleoli with infrequent, moderately pleomorphic and hyperchromatic cells. These lesions show myofibroblastic differentiation with expression of smooth-muscle markers and occasional keratin expression. Myofibroblastic differentiation is also seen in ultrastructural studies. The features that can be used to distinguish inflammatory pseudotumor from a sarcoma are:

■ areas of the lesion resembling granulation tissue
■ mitotic figures infrequent
■ less pleomorphism
■ prominent myxoid change
■ recurrence rare following incomplete excision.

Benign phyllodes tumor vs cystosarcoma

As an incidental finding within prostate specimens, small fibroadenoma-like foci can sometimes be observed in the prostate. Larger lesions have been reported as *benign phyllodes tumor or fibroadenoma*. In such lesions, the prostatic epithelium may be compressed into slit-like spaces, as in intracanalicular fibroadenoma of the breast, or the prostatic epithelium may line cystic structures into which project papillary finger-like areas of stroma lined by a prostatic epithelium. The stroma in cases reported as fibroadenoma or benign phyllodes tumor is composed of hyperplastic smooth-muscle and fibrous tissue without atypia of mitoses[443] (Figure 4.26(A)).

Malignant cystosarcoma phyllodes of the prostate differ from benign phyllodes tumor[447] and atypical stromal hyperplasia in that the stroma shows:

■ cytologic atypia
■ increased mitoses
■ infiltrative pattern
■ outstripping of the epithelial component by the neoplastic stroma.

Only a handful of these cases has been reported with limited follow-up. Several of the malignant cystosarcoma phyllodes of the prostate have persisted or progressed following limited surgery.

Additional lesions with spindle cell appearance

Leiomyoma of the prostate is another unusual prostatic spindle cell lesion. Histologically the lesion is composed of a well-circumscribed mass of smooth muscle cell proliferation in prostatic or juxtaprostatic tissue that is devoid of epithelial elements and reaches 1 cm or more in diameter. No specific histologic criterion exists to differentiate

a leiomyoma from a leiomyosarcoma of the prostate as opposed to smooth muscle tumors of the uterus.[442] However, the following features appear to be of utmost importance for the diagnosis of *leiomyosarcoma* (Figure 4.26(B)):

- evidence of invasion
- high cellularity
- pleomorphism
- increased mitotic activity.

The definition of 'atypical leiomyoma' of the prostate is used by some authors to refer to well-circumscribed lesions with a variable amount of nuclear atypia (Figure 4.26(C)) and scattered mitotic activity. Although most atypical leiomyomas have shown no evidence of disease with short follow-up, a few have recurred.[442] Because smooth-muscle tumors of the prostate are rare, the criteria for distinguishing between leiomyosarcoma and leiomyoma in these cases with borderline features have not been elucidated.

Prostatic blue nevus is a peculiar spindle cell proliferation containing melanin within fibromuscular prostatic stroma.[448] This histologic appearance is reminiscent of the common blue nevus of the skin (Figure 4.26(D)). It is believed that this lesion does not transform into melanoma, in contrast to the cellular blue nevus, which occasionally undergoes malignant transformation. The terms blue nevus and melanosis of the prostate are occasionally used interchangeably, although most researchers refer to melanosis when melanin is present within both the glandular and stromal melanocytes.

fibromuscular nodules in which smooth muscle typically predominates, and in leiomyomas. It is important to be aware that malignant neoplasms of the prostate, such as in frank sarcomas and mixed epithelial-stromal tumors, may contain *atypical stromal cells* similar to those that can be seen either in nodular hyperplasia or fibromuscular nodules.[448] The distinction of the latter two entities from the former depends on:

- the absence of a mass
- the lack of stromal hypercellularity or phyllodes-type architecture
- the degenerative nuclear appearance with smuggled chromatin
- the lack of mitoses.

Distinction of degenerative stromal atypia from the atypicality seen with neoplasms may be very difficult in a limited sampling, and, as suggested by Gaudin and colleagues, the designation 'prostatic stromal proliferation of uncertain malignant potential' can be justified in such cases to alert the clinician to this uncertainty.[442,449]

Miscellaneous sarcomas

Rare cases of malignant fibrous histiocytoma,[450–454] angiosarcoma,[455] osteosarcoma,[456,457] chondrosarcoma,[458] malignant peripheral nerve sheath tumors,[459] and synovial sarcoma have been reported.[460]

Atypical stromal cells

Pleomorphic, hyperchromatic nuclei may be seen in the prostatic stroma cells between the epithelial elements in otherwise unremarkable cases of benign prostatic hyperplasia, in circumscribed benign

Part 13

Miscellaneous, secondary, and lymphoid tumors of the prostate

Miscellaneous tumors

This is a very heterogeneous group of tumors which are very rarely observed in the prostate: cystadenoma,[461,462] Wilms' tumor (nephroblastoma),[463] malignant rhabdoid tumor,[464] clear cell adenocarcinoma,[465,466] melanoma of the prostate,[467] paraganglioma,[468,469] and neuroblastoma.[470]

Secondary tumors

Metastatic tumors arise outside of the prostate and spread to the gland by vascular channels. Contiguous spread from other pelvic tumors into the prostate does not constitute a metastasis. Metastases from lung, skin (melanoma), gastrointestinal tract, kidney, testis, and endocrine glands have been reported.[471,472] Clinical context, morphologic features, and immunocytochemical localization of PSA and PSAP clarify the differential diagnosis. Prognosis reflects the late stage of disease in which prostatic metastases are seen. Lymphoid tumors of the prostate are discussed separately.

Lymphoid tumors

The prostate is a rare site of extranodal lymphoma with a total of 165 cases arising in or secondarily involving the prostate reported. Of patients with chronic lymphocytic leukemia, 20% are reported to have prostate involvement at autopsy.[473] Rarely Hodgkin's lymphoma and mucosa-associated lymphoid tissue (MALT) lymphoma have been reported.[474,475] In a recent large series of 62 cases, 22, 30, and 10 cases were classified as primary, secondary, and indeterminate, respectively. Sixty cases were non-Hodgkin's (predominately diffuse large cell followed by small lymphocytic lymphoma). Most frequent symptoms are those related to lower urinary obstruction.

Part 14

Appendices

Handling of prostate biopsies

- The most common fixative used for needle biopsies is formalin, although alternative fixatives which enhance nuclear details are also in use. A potential problem with these alternative fixatives is that lesions such as high-grade prostatic intraepithelial neoplasia may be overdiagnosed.
- Prostate biopsies from different regions of the gland should be identified separately, i.e., the core biopsies from each site are submitted in separate containers (see below).
- If two cores are taken from the same region, they can be placed into the same block. However, blocking more than two biopsy specimens together increases the loss of tissue at sectioning.[476]
- All blocks are sectioned at 3 μm and are stained with haematoxylin and eosin (H&E). In particular, all cores are sectioned in three separate levels represented on separate slides, with each slide containing at least three serial sections. Submit slides 1 and 3 to standard staining and keep the intervening unstained sections of the slide of level 2 for immunohistochemistry. The increase in cost due to additional slides can be bypassed by storing ribbons of unstained levels until standard stains are examined. Even, if this procedure leads to a small increase in costs as far as slides and technician time are concerned, there is a definite benefit in that there is no need to recut new sections, no delay in pathology report, and, furthermore, a less frequent disappearance of the suspicious focus on subsequent pathology sections. Intervening slides are critical to establish a conclusive diagnosis in 2.8% of prostate biopsies, hence sparing a repeat biopsy.[477]

Site of sampling (specific location of the biopsy)

The potential importance of knowing the specific location of the biopsy and, by extension, the location of cancer may be summarized as follows[312,478,479] (Table 4.33):

> **Table 4.33** The potential importance of knowing the specific location of the biopsy and the location of cancer
>
> - Correlation with digital rectal examination and imaging studies
> - Prognostic importance
> - Importance in planning therapy
> - Importance in subsequent patient sampling
> - Importance in subsequent prostate gland sampling
> - Technical superiority in needle biopsy material examination
> - Knowledge of biopsy site helps recognize potential diagnostic pitfalls

- *Correlation with digital rectal examination and imaging studies.*
- *Prognostic importance.* Tumor involvement of base biopsies may influence bladder neck sparing radical prostatectomy; extensive cancer in base biopsies correlates with extraprostatic extension; and dominant side of prostate biopsy correlates with ipsilateral positivity of surgical margins and extraprostatic extension.
- *Importance in planning therapy.* Mapping distribution of the cancer in needle biopsies may help plan the field of radiation therapy or may influence nerve sparing or bladder neck sparing during radical prostatectomy.
- *Importance in subsequent patient sampling.* In a patient with atypical glands without cancer, knowledge of site allows for more focused repeat biopsies.
- *Importance in subsequent prostate gland sampling.* Biopsy samples with site-specific labeling usually contain only one or two cores, which is advantageous for block and slide preparation and allows for complete visualization of cores and detection of small foci of cancer; and knowledge of location of cancer may help target additional tissue or block sampling in cases with no apparent cancer in radical prostatectomy sections.
- *Knowledge of biopsy site helps recognize potential diagnostic pitfalls.* This includes seminal vesicle epithelium or central zone epithelium, seen most frequently in base biopsies and the rare Cowper's glands in apex biopsies.

Handling of TURP specimens

A TURP specimen may contain more than a hundred grams of tissue and it is often necessary to select a limited amount of tissue for histologic examination. Submission should be random to ensure that the percentage of the specimen area involved with cancer is representative for the entire specimen. Several strategies for selection have been evaluated. Submission of eight cassettes will identify almost all stage T1b cancers and approximately 90% of stage T1a tumors.[480,481] In young men, submission of the entire specimen may be considered to ensure detection of all T1a tumors. Guidelines have been developed for whether additional sampling is needed following the initial detection of cancer in a TURP specimen.[482]

Handling of radical prostatectomy specimens (Table 4.34 and Figure 4.27)

- Weight and size. The fresh (unfixed) radical prostatectomy (RP) specimen is weighed and may be measured in three dimensions, e.g., width, height, and length. The volume of the specimen is

Table 4.34 Macroscopic examination

1. Specimen
   a. Organ(s)/tissues included
   b. Unfixed/fixed (specify fixative)
   c. Opened/unopened
   d. Orientation (if indicated by surgeon)
   e. Structures included in specimen
      – prostate
      – seminal vesicles
      – segments of vasa deferentia
      – bladder neck
      – urethra
      – other(s) (specify)
   f. Size (three dimensions)
   g. Weight (prostate separately)
   h. Obstruction of urethra (partial/complete)
   i. Descriptive features (e.g. nodular hyperplasia)
   j. Results of intraoperative consultation

2. Tumor (if identified)
   a. Location(s)
   b. Size(s)
   c. Descriptive features
   d. Extent of local invasion

3. Regional lymph nodes
   a. Location
   b. Number (each location, if possible)

4. Blocks submitted for microscopic evaluation
   a. Tumor(s) (each grossly recognizable tumor)
   b. Blocks from other anatomic locations within the prostate (to evaluate for multicentricity)
   c. Blocks to determine extent of invasion
      – prostatic capsule and periprostatic tissue adjacent to each tumor including inked margins
      – seminal vesicles
      – periprostatic tissue at bases of seminal vesicles
   d. Apex
   e. Prostate base margin
   f. All lymph nodes
   g. Frozen section tissue fragment(s) (unless saved for special studies)
   h. Other tissues (specify)

5. Special studies (specify) (e.g. immunohistochemistry, ploidy analysis, S-phase fraction)

calculated as the volume of an ellipse:[483] (width × height × length) × 0.523.

■ The entire surface of the RP specimen is inked using two different colors for each side in order to recognize the left and right. Green and red (or blue) are commonly used. The India ink could be preferred to the two-color procedure because the black colored margins are more easily identified when the sections are examined under the microscope. By immersing the inked gland into a mordant, such as Bouin's solution or acetic acid, the ink is fixed to the surface.[243]

■ Unless fresh tissue is harvested for research purposes, it is better to fix the prostate before sectioning, which results in thinner sections and a better assessment of the margins of resection. In order to reduce the fixation time and to enhance a quick and uniform penetration of the fixative, the prostate specimen is injected with 10% neutral-buffered formalin solution using a fine hypodermic needle (0.6 × 25 mm, for instance). After

plunging the needle deep into the prostatic tissue, formalin solution is slowly injected while the needle is slowly retracted. Formalin injection is performed in a systematic way, at multiple 0.5-cm spaced sites at all sides of the RP specimen. In total, approximately 100 ml of formalin solution is injected.[353]

■ The RP specimen is then immersed in 300–400-ml formalin solution and allowed to fix for 24 hours.

■ Sectioning procedure:

   – The seminal vesicles (SVs) are removed from the RP specimen. The seminal vesicles are analyzed by taking a section through the base of the seminal vesicle where the seminal vesicle joins the prostate.[347]
   – The apical and basal parts of the prostate are removed by a transversal cut at 4 mm from the distal and proximal margins, respectively. Optionally, the distal urethral margin may be removed from the apical part and examined separately. The apical and proximal parts are then sectioned as follows: slices are cut parasagittally at 4-mm intervals and perpendicularly to the inked surface.
   – The prostate specimen is step-sectioned at 3- to 4-mm intervals perpendicular to the long axis (apical–basal) of the gland. A slicing machine should be used. Serial coronal sections, parallel to an initial *en-face* section of the apex, are taken until the junction of the seminal vesicles is approached. The whole-mount sections are identified in a consecutive manner with capital letters, always starting from the most apical section. In this way, the whole RP specimen is available for histologic examination.[484] When the India ink is used, a cut is made with a scalpel in the right antero-lateral aspect of each slice to mark the right side.

■ The cut specimen may be post-fixed for 24 hours. The *en-face* section is then processed as a single section; alternatively, the *en-face* sections are submitted as quadrants following a systematic numbering scheme. In particular, the cut specimen is dehydrated in graded alcohols, cleared in xylene, embedded in paraffin, and examined histologically as 5 μm-thick, whole-mount, H&E-stained sections. Special molding and inclusion cassettes should be used. The slides should be at least 76 mm long and 50 mm wide. Cover-slips of a similar size have to be used.[345,484] The dilemma of choosing between whole mount sections and quadrant sections is one of balancing aesthetics and greater ease in examining sections against the cost of time and materials and the logistic problem of storing glass slides and paraffin blocks of unconventional size. The only significant difference in the histopathology of these two different processing methods is that whole mounts are often thicker sections. In addition, immunohistochemistry will require larger amounts of reagents and can only be performed manually.[345]

Handling of pT0 radical prostatectomies (i.e., search for residual cancer)

Searching protocol on RPs that initial routine-based examination does not show residual cancer, i.e., pT0.[485] In particular, the following steps are undertaken by two pathologists:

1. The diagnostic needle biopsies are reviewed to exclude the possibility of a false positive biopsy diagnosis and to assess the
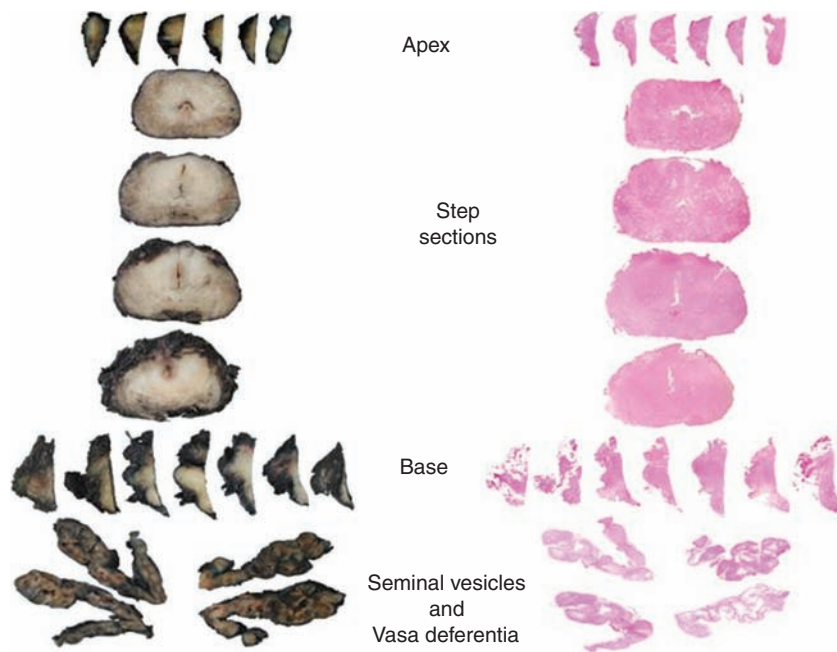
approximate location of the biopsy with tumor, such as apex, mid-zone, and base, both left and right.

2. The slides of the surgical specimens are reviewed for residual cancer that was initially overlooked or missed.

3. If the prostate is not totally embedded, the remaining prostate tissue is processed in toto. This type of information is usually contained in the pathology form. This information is further confirmed by searching the specimen's container for residual pieces.

4. Serial sections of the prostatectomy area corresponding to the location of the core with cancer are recut. Further sections are also obtained from all the other paraffin blocks.

5. Serial sections of the area corresponding to the location of the positive core as well as of all the remaining blocks are recut after block-flipping.

6. Immunostains for p63 and alpha-methylacyl-CoA racemase (AMACR) are performed to evaluate suspicious foci.

7. Immunostain for cytokeratin CAM 5.2 p63 and PSA is performed to identify the so-called 'minimal residual cancer', especially in patients receiving neoadjuvant hormonal therapy.[494]

8. Review the description of the macroscopic appearance of external and cut surfaces of the surgical specimen as well as inspect the contour of the tissue sections on the slides for hint or clues that might indicate that part of the tissue is missing either due to the surgical procedure or for technical reasons.

9. DNA specimen analysis is performed on formalin-fixed tissue to confirm the identity of the biopsies and prostatectomies, whenever necessary.

References

1. Srigley JR, Amin MB, Boccon-Gibod L et al. Prognostic and predictive factors in prostate cancer: historical perspectives and recent international consensus initiatives. Scand J Urol Nephrol 2005; 216: 8–19.

2. Nelson WG, De Marzo AM, Isaacs WB. Prostate cancer. N Engl J Med 2003; 349: 366–81.

3. Crawford ED. Epidemiology of prostate cancer. Urology 2003; 62: 3–12.

4. Gonzalgo ML, Isaacs WB. Molecular pathways to prostate cancer. J Urol 2003; 170: 2444–52.

5. Visakorpi T. The molecular genetics of prostate cancer. Urology 2003; 62: 3–10.

6. Orteil H. Involutionary changes in prostate and female breast cancer in relation to cancer development. Can Med Assoc J 1926; 16: 237.

7. Andrews GS. Latent carcinoma of the prostate. J Clin Pathol 1949; 2: 197.

8. Kastendieck H, Helpap B. Prostatic 'dysplasia/atypical hyperplasia'. Urology 1989; 24: 28–42.

9. McNeal JE. Morphogenesis of prostatic carcinoma. Cancer 1965; 18: 1659–66.

10. McNeal JE, Bostwick DG. Intraductal dysplasia: a premalignant lesion of the prostate. Hum Pathol 1986; 17: 64–71.

11. Bostwick DG, Brawer MK. Prostatic intra-epithelial neoplasia and early invasion in prostate cancer. Cancer 1987; 59: 788–94.

12. Bostwick DG. Prostatic intraepithelial neoplasia (PIN). Urology 1989; 34: 16–22.

13. Berman DM, Yang J, Epstein JI. Foamy gland high-grade prostatic intraepithelial neoplasia. Am J Surg Pathol 2000; 24: 140–4.

14. Reyes AO, Swanson PE, Carbone JM et al. Unusual histologic types of high grade prostatic intraepithelial neoplasia. Am J Surg Pathol 1997; 21: 1215–22.

15. Bostwick DG, Amin MB, Dundore P et al. Architectural patterns of high grade prostatic intraepithelial neoplasia. Hum Pathol 1993; 24: 298–310.

16. Qian J, Wollan P, Bostwick DG. The extent and multicentricity of high-grade prostatic intraepithelial neoplasia in clinically localized prostatic adenocarcinoma. Hum Pathol 1997; 28: 143–8.

17. da Silva VD, Montironi R, Thompson D et al. Chromatin texture in high grade prostatic intraepithelial neoplasia and early invasive carcinoma. Anal Quant Cytol Histol 1999; 21: 113–20.

18. McNeal JE. The significance of duct-acinar dysplasia in prostatic carcinogenesis. Prostate 1988; 13: 91–102.

19. McNeal JE, Villers A, Redwine EA et al. Microcarcinoma in the prostate: its association with duct-acinar dysplasia. Hum Pathol 1991; 22: 644–52.

20. McNeal JE, Haillot O, Yemoto C. Cell proliferation in dysplasia of the prostate: analysis by PCNA immunostaining. Prostate 1995; 27: 258–68.

21. Montironi R, Thompson D, Bartels PH. Premalignant lesions of the prostate. In: Lowe DG, Underwood JCE, eds. Recent Advances in Histopathology Edinburgh, UK: Churchill Livingstone; 1999; 147–72.

22. Qian J, Jenkins RB, Bostwick DG. Detection of chromosomal anomalies and c-myc gene amplification in the cribriform pattern of prostatic intraepithelial neoplasia and carcinoma by fluorescence in situ hybridization. Mod Pathol 1997; 10: 1113–19.

23. Qian J, Bostwick DG, Takahashi S et al. Chromosomal anomalies in prostatic intraepithelial neoplasia and carcinoma detected by fluorescence in situ hybridization. Cancer Res 1995; 55: 5408–14.

24. Epstein JI, Cho KIR, Quinn BD. Relationship of severe dysplasia to stage A (incidental) adenocarcinoma of the prostate. Cancer 1990; 65: 2321–7.

25. Quinn BD, Cho KR, Epstein JI. Relationship of severe dysplasia to stage B adenocarcinoma of the prostate. Cancer 1990; 65: 2328–37.

26. Sakr WA, Grignon DJ, Haas GP et al. Age and racial distribution of prostatic intraepithelial neoplasia. Eur Urol 1996; 30: 138–44.

27. Gaudin PB, Sesterhenn IA, Wojno KJ et al. Incidence and clinical significance of high-grade prostatic intraepithelial neoplasia in TURP specimens. Urology 1997; 49: 558–63.

28. Harvei S, Skjorten FJ, Robsahm TE et al. Is prostatic intraepithelial neoplasia in the transition/central zone a true precursor of cancer? A long-term retrospective study in Norway. Br J Cancer 1998; 78: 46–9.

29. Pacelli A, Bostwick DG. Clinical significance of high-grade prostatic intraepithelial neoplasia in transurethral resection specimens. Urology 1997; 50: 355–9.

30. Kovi J, Jackson MA, Heshmat MY. Ductal spread in prostatic carcinoma. Cancer 1985; 56: 1566–73.

31. Allam CK, Bostwick DG, Hayes JA et al. Interobserver variability in the diagnosis of high-grade prostatic intraepithelial neoplasia and adenocarcinoma. Mod Pathol 1996; 9: 742–51.

32. Epstein JI, Grignon DJ, Humphrey PA et al. Interobserver reproducibility in the diagnosis of prostatic intraepithelial neoplasia. Am J Surg Pathol 1995; 19: 873–86.

33. Montironi R, Mazzucchelli R, Bostwick DG et al. Recent advances in the quantitative morphological evaluation of prostate neoplasia. J Urol Pathol 2000; 12: 133–68.

34. Montironi R, Mazzucchelli R, Santinelli A et al. Case diagnosis as positive identification in prostatic neoplasia. Anal Quant Cytol Histol 1998; 20: 424–36.

35. Mettlin C, Lee F, Drago J et al. The American Cancer Society National Prostate Cancer Detection Project. Findings on the detection of early prostate cancer in 2425 men. Cancer 1991; 67: 2949–58.

36. Lee F, Torp-Pedersen ST, Carroll JT et al. Use of transrectal ultrasound and prostate-specific antigen in diagnosis of prostatic intraepithelial neoplasia. Urology 1989; 24: 4–12.

37. Haddad FS. Risk factors for perineal seeding of prostate cancer after needle biopsy. J Urol 1990; 143: 587–8.

38. Davidson D, Bostwick DG, Qian J et al. Prostatic intraepithelial neoplasia is a risk factor for adenocarcinoma: predictive accuracy in needle biopsies. J Urol 1995; 154: 1295–9.

39. Aboseif S, Shinohara K, Weidner N et al. The significance of prostatic intra-epithelial neoplasia. Br J Urol 1995; 76: 355–9.

40. Berner A, Danielsen HE, Pettersen EO et al. DNA distribution in the prostate. Normal gland, benign and premalignant lesions, and subsequent adenocarcinomas. Anal Quant Cytol Histol 1993; 15: 247–52.

41. Bostwick DG, Iczkowski KA. Minimal criteria for the diagnosis of prostate cancer on needle biopsy. Ann Diagn Pathol 1997; 1: 104–29.

42. Brawer MK, Bigler SA, Sohlberg OE et al. Significance of prostatic intraepithelial neoplasia on prostate needle biopsy. Urology 1991; 38: 103–7.

43. Keetch DW, Humphrey P, Stahl D et al. Morphometric analysis and clinical follow-up of isolated prostatic intraepithelial neoplasia in needle biopsy of the prostate. J Urol 1995; 154: 347–51.

44. Langer JE, Rovner ES, Coleman BG et al. Strategy for repeat biopsy of patients with prostatic intraepithelial neoplasia detected by prostate needle biopsy. J Urol 1996; 155: 228–31.

45. Markham CW. Prostatic intraepithelial neoplasia. Detection and correlation with invasive cancer in fine-needle biopsy. Urology 1989; 24: 57–61.

46. Raviv G, Zlotta AR, Janssen T et al. Do prostate specific antigen and prostate specific antigen density enhance the detection of prostate carcinoma after initial diagnosis of prostatic intraepithelial neoplasia without concurrent carcinoma? Cancer 1996; 77: 2103–8.

47. Shepherd D, Keetch DW, Humphrey PA et al. Repeat biopsy strategy in men with isolated prostatic intraepithelial neoplasia on prostate needle biopsy. J Urol 1996; 156: 460–3.

48. Raviv G, Janssen TH, Zlotta AR et al. Prostatic intraepithelial neoplasia: influence of clinical and pathological data on the detection of prostate cancer. J Urol 1996; 156: 1050–4.

49. Kelloff GJ, Boone CW, Crowell JA et al. Surrogate endpoint biomarkers for phase II cancer chemoprevention trials. J Cell Biochem 1994; 19: 1–9.

50. Cohen RJ, McNeal JE, Baillie T. Patterns of differentiation and proliferation in intraductal carcinoma of the prostate: significance for cancer progression. Prostate 2000; 43: 11–19.

51. McNeal JE, Yemoto CE. Spread of adenocarcinoma within prostatic ducts and acini. Morphologic and clinical correlations. Am J Surg Pathol 1996; 20: 802–14.

52. Rubin MA, de La TA, Bagiella E et al. Cribriform carcinoma of the prostate and cribriform prostatic intraepithelial neoplasia: incidence and clinical implications. Am J Surg Pathol 1998; 22: 840–8.

53. Wilcox G, Soh S, Chakraborty S et al. Patterns of high-grade prostatic intraepithelial neoplasia associated with clinically aggressive prostate cancer. Hum Pathol 1998; 29: 1119–23.

54. Epstein JI, Yang XJ. Prostatic duct adenocarcinoma. In: Epstein JI, Yang XJ, eds. Prostate Biopsy Interpretation, 3rd edn. Philadelphia PA: Lippincott Williams & Wilkins, 2002.

55. Montironi R, Hamilton PW, Scarpelli M et al. Subtle morphological and molecular changes in normal-looking epithelium in prostates with prostatic intraepithelial neoplasia or cancer. Eur Urol 1999; 35: 468–73.

56. Bostwick DG, Cheng L. Overdiagnosis of prostatic adenocarcinoma. Semin Urol Oncol 1999; 17: 199–205.

57. Bostwick DG, Srigley J, Grignon D et al. Atypical adenomatous hyperplasia of the prostate: morphologic criteria for its distinction from well-differentiated carcinoma. Hum Pathol 1993; 24: 819–32.

58. Helpap B, Bonkhoff H, Cockett A et al. Relationship between atypical adenomatous hyperplasia (AAH), prostatic intraepithelial neoplasia (PIN), and prostatic adenocarcinoma. Pathologica 1997; 89: 288–300.

59. Cheng L, Shan A, Cheville JC et al. Atypical adenomatous hyperplasia of the prostate: a premalignant lesion? Cancer Res 1998; 58: 389–91.

60. De Marzo AM, Marchi VL, Epstein JI et al. Proliferative inflammatory atrophy of the prostate: implications for prostatic carcinogenesis. Am J Pathol 1999; 155: 1985–92.

61. Amin M, Boccon-Gibod L, Egevad L et al. Prognostic and predictive factors and reporting of prostate carcinoma in prostate needle biopsy specimens. Scand J Urol Nephrol 2005; 216: 20–33.

62. Boccon-Gibod L, van der Kwast TH, Montironi R et al. European Society of Uropathology; European Society of Pathology Uropathology Working Group. Handling and pathology reporting of prostate biopsies. Eur Urol 2004; 46: 177–81.

63. Cheville JC, Reznicek MJ, Bostwick DG. The focus of 'atypical glands, suspicious for malignancy' in prostatic needle biopsy specimens: incidence, histologic features, and clinical follow-up of cases diagnosed in a community practice. Am J Clin Pathol 1997; 108: 633–40.

64. Epstein J, Herawi M. Prostate needle biopsies containing Prostatic Intraepithelial Neoplasia or atypical foci suspicious for carcinoma: implications for patient care. J Urol 2006; 175; 820–34.

65. Iczkowski KA, MacLennan GT, Bostwick DG. Atypical small acinar proliferation suspicious for malignancy in prostate needle biopsies: clinical significance in 33 cases. Am J Surg Pathol 1997; 21: 1489–95.

66. Schlesinger C, Bostwick DG, Iczkowski KA. High grade prostatic intraepithelial neoplasia and atypical small acinar proliferation: predictive value for cancer in current practice. Am J Surg Pathol 2005; 29: 1201–7.

67. Epstein JI, Yang XJ. Finding of atypical glands suspicious for cancer. In: Epstein JI, Yang XJ, eds. Prostate Biopsy Interpretation. Chicago, IL: Lippincott Williams & Wilkins; 2002; 177–84.

68. Epstein JI. Atypical small acinar proliferation of the prostate gland. Am J Surg Pathol 1998; 22: 1430–1.

69. Murphy WM. ASAP is a bad idea. Human Pathol 1999; 30: 601.

70. Wightman HR. Atypical small acinar proliferation of the prostate gland. Am J Surg Pathol 1999; 23: 489–91.

71. Borboroglu PG, Sur RL, Roberts JL et al. Repeat biopsy strategy in patients with atypical small acinar proliferation or high grade prostatic intraepithelial neoplasia on initial prostate needle biopsy. J Urol 2001; 166: 866–70.

72. Bostwick DG, Qian J, Frankel K. The incidence of high-grade prostatic intraepithelial neoplasia in needle biopsies. J Urol 1995; 154: 1791–4.

73. Brausi M, Castagnetti G, Dotti A et al. Immediate radical prostatectomy in patients with atypical small acinar proliferation: overtreatment? J Urol 2004; 172: 906–8.

74. Fadare O, Wang S, Mariappan MR. Practice patterns of clinicians following isolated diagnoses of atypical small acinar proliferation on prostate biopsy specimens. Arch Pathol Lab Med 2004; 128: 557–60.

75. Gupta C, Ren JZ, Wojno KJ. Individual submission and embedding of prostate biopsies decreases rates of equivocal pathology reports. Urology 2004; 63: 83–6.

76. Hoedemaeker RF, Kranse R, Rietbergen JB et al. Evaluation of prostate needle biopsies in a population based screening study: the impact of borderline lesions. Cancer 1999; 85: 145–52.

77. Iczkowski KA, Chen HM, Yang XJ et al. Prostate cancer diagnosed after initial biopsy with atypical small acinar proliferation suspicious for malignancy is similar to cancer found on initial biopsy. Urology 2002; 60: 851–4.

78. Kahane H, Sharp JW, Shuman GB et al. Utilization of high molecular weight cytokeratin on prostate needle biopsies in an independent laboratory. Urology 1995; 45: 981–6.

79. Kobayashi T, Nishizawa K, Watanabe J et al. Effects of sextant transrectal prostate biopsy plus additional far lateral cores in improving cancer detection rates in men with large prostate glands. Int J Urol 2004; 11: 392–6.

80. Naya Y, Ayala AG, Tamboli P et al. Can the number of cores with high-grade prostate intraepithelial neoplasia predict cancer in men who undergo repeat biopsy? Urology 2004; 63: 503–8.

81. Novis DA, Zarbo RJ, Valenstein, PA. Diagnostic uncertainty expressed in prostate needle biopsies. A College of American Pathologists Q-probes Study of 15,753 prostate needle biopsies in 332 institutions. Arch Pathol Lab Med 1999; 123: 687–92.

82. O'dowd GJ, Miller MC, Orozco R et al. Analysis of repeated biopsy results within 1 year after a noncancer diagnosis. Urology 2000; 55: 553–9.

83. Ouyang RC, Kenwright DN, Nacey JN, Delahunt B. The presence of atypical small acinar proliferation in prostate needle biopsy is predictive of carcinoma on subsequent biopsy. BJU Int 2001; 87: 70–4.

84. Postma R, Roobol M, Schroder FH et al. Lesions predictive for prostate cancer in a screened population: first and second screening round findings. Prostate 2004; 61: 260–6.

85. Renshaw AA, Santis WF, Richie JP. Clinicopathological characteristics of prostatic adenocarcinoma in men with atypical prostate needle biopsies. J Urol 1998; 159: 2018–21.

86. Roehrborn CG, Pickens GJ, Sanders JS. Diagnostic yield of repeated transrectal ultrasound-guided biopsies stratified by specific histopathologic diagnoses and prostate specific antigen levels. Urology 1996; 47: 347–52.

87. Weinstein MH, Greenspan DL, Epstein JI. Diagnoses rendered on prostate needle biopsy in community hospitals. Prostate 1998; 35: 50–5.

88. Wills ML, Hamper UM, Partin AW et al. Incidence of high-grade prostatic intraepithelial neoplasia in sextant needle biopsy specimens. Urology 1997; 49: 367–73.

89. Chan TY, Epstein JI. Follow-up of atypical prostate needle biopsies suspicious for cancer. Urology 1999; 53: 351–5.

90. Iczkowski KA, Bassler TJ, Schwob VS et al. Diagnosis of 'suspicious for malignancy' in prostate biopsies: predictive value for cancer. Urology 1998; 51: 749–57.

91. Park S, Shinohara K, Grossfeld GD et al. Prostate cancer detection in men with prior high grade prostatic intraepithelial neoplasia or atypical prostate biopsy. J Urol 2001; 165: 1409–14.

92. Samaratunga H, Gardiner RA, Yaxley J et al. Atypical prostatic glandular proliferation on needle biopsy: diagnostic implications, use of immunohistochemistry, and clinical significance. Anal Quant Cytol Histol 2006; 28: 104–10.

93. Srigley JR. Small-acinar patterns in the prostate gland with emphasis on atypical adenomatous hyperplasia and small-acinar carcinoma. Semin Diagn Pathol 1988; 5: 254–72.

94. Epstein JI. Diagnostic criteria of limited adenocarcinoma of the prostate on needle biopsy. Hum Pathol 1995; 26: 223–9.

95. Herawi M, Parwani T, Irie J et al. Small glandular proliferations on needle biopsies; most common benign mimickers of prostatic adenocarcinoma sent in for expert second opinion. Am J Surg Pathol 2005; 29: 874–80.

96. Iczkowski KA, Bostwick DG. Criteria for biopsy diagnosis of minimal volume prostatic adenocarcinoma: analytic comparison with nondiagnostic but suspicious atypical small acinar proliferation. Arch Pathol Lab Med 2000; 124: 98–107.

97. Kronz JD, Shaikh AA, Epstein JI. High-grade prostatic intraepithelial neoplasia with adjacent small atypical glands on prostate biopsy. Hum Pathol 2001; 32: 389–95.

98. Mai K, Yazdi HM, Belanger E et al. High-grade prostatic intraepithelial neoplasia involving small ducts and acini. Histopathology 2005; 46: 475–7.

99. Signoretti S, Waltregny D, Dilks J et al. p63 is a prostate basal cell marker and is required for prostate development. Am J Pathol 2000; 157: 1769–75.

100. Ramnani DM, Bostwick DG. Basal cell-specific anti-keratin antibody 34betaE12: optimizing its use in distinguishing benign prostate and cancer. Mod Pathol 1999; 12: 443–4.

101. Montironi R, Vela-Navarrete R, Lopez-Beltran A. 2005 update on pathology of prostate biopsies with cancer. Eur Urol 2006; 49: 241–7.

102. Shah RB, Zhou M, LeBlanc M et al. Comparison of the basal cell specific markers, 34betaE12 and p63 in the diagnosis of prostate cancer. Am J Surg Pathol 2002; 26: 1161–8.

103. Hendrik L, Epstein JI. Use of keratin 903 as an adjunct in the diagnosis of prostate carcinoma. Am J Surg Pathol 1989; 13: 389–96.

104. Parsons JK, Gage WR, Nelson WG et al. p63 protein expression is rare in prostate adenocarcinoma: implications for cancer diagnosis and carcinogenesis. Urology 2001; 58: 619–24.

105. Shah RB, Kunju LP, Shen R et al. Usefulness of basal cell cocktail (34betaE12 + p63) in the diagnosis of atypical prostate glandular proliferations. Am J Clin Pathol 2004; 122: 517–23.

106. Zhou M, Shah R, Ronglai S et al. Basal cell cocktail (34betaE12 + p63) improves the detection of prostate basal cells. Am J Surg Pathol 2003; 27: 365–71.

107. Zhou M, Aydin H, Kanane H et al. How often does alpha-methylacyl-CoA-racemase contribute to resolving an atypical diagnosis on prostate needle biopsy. Beyond that provided by basal cell markers. Am J Surg Pathol 2004; 28: 239–43.

108. Hameed O, Sublett J, Humphrey PA. Immunohistochemical stains for p63 and alpha-methylacyl-CoA racemase, versus a cocktail comprising both, in the diagnosis of prostatic carcinoma: a comparison of the immunohistochemical staining of 430 foci in radical prostatectomy and needle biopsy tissues. Am J Surg Pathol 2005; 29: 579–87.

109. Scattoni V, Roscigno M, Freschi M et al. Predictors of prostate cancer after initial diagnosis of atypical small acinar proliferation at 10 to 12 core biopsies. Urology 2005; 66: 1043–7.

110. Moore CK, Karikehalli S, Nazeer T et al. Prognostic significance of high grade prostatic intraepithelial neoplasia and atypical small acinar proliferation in the contemporary era. J Urol 2005; 173: 70–2.

111. Girasole CR, Cookson MS, Putzi MJ et al. Significance of atypical and suspicious small acinar proliferation, and high grade prostatic intraepithelial neoplasia on prostate biopsy: implication for cancer detection and biopsy strategy. J Urol 2006; 175: 929–33.

112. Zhang PL, Shuffler SH, Bihrle W III et al. Subclassification of small atypical glands in prostate biopsies provides a clearer indication for re-biopsies. Mod Pathol 2000; 13: 105A.

113. Keane PF, Ilesley IC, O'Donoghue PN et al. Pathological classification and follow-up of prostatic lesions initially diagnosed as 'suspicious of malignancy'. Br J Urol 1990; 66: 306–11.

114. Descazeaud A, Rubin MA, Allory Y et al. What information are urologists extracting from prostate needle biopsy reports and what do they

need for clinical management of prostate cancer? Eur Urol 2005; 48: 911–15.

115. Leite KR, Mitteldorf CA, Camara-Lopes LH. Repeat prostate biopsies following diagnoses of prostate intraepithelial neoplasia and atypical small gland proliferation. Int Braz J Urol 2005; 31: 131–6.

116. Humphrey PA. Focal glandular atypia. In: Humphrey PA, ed. Prostate Pathology. Chicago, IL: ASCP Press; 2003: 219–25.

117. Allen EA, Kahane H, Epstein JI. Repeat biopsy strategies for men with atypical diagnoses on initial prostate needle biopsy. Urology 1998; 52: 803–7.

118. Ellis WJ, Brawer MK. Repeat prostate needle biopsy: who needs it? J Urol 1995; 153: 1496–8.

119. Hamper UM, Sheth S, Walsh PC et al. Stage B adenocarcinoma of the prostate: transrectal US and pathologic correlation of nonmalignant hypoechoic peripheral zone lesions. Radiology 1991; 180: 101–4.

120. Dahnert WF, Hamper UM, Eggleston JC et al. Prostatic evaluation by transrectal sonography with histopathologic correlation: the echopenic appearance of early carcinoma. Radiology 1986; 158: 97–102.

121. Salo JO, Rannikko S, Makinen J et al. Echogenic structure of prostatic cancer imaged on radical prostatectomy specimens. Prostate 1987; 10: 1–9.

122. Hamper UM, Sheth S, Walsh PC et al. Bright echogenic foci in early prostatic carcinoma: sonographic and pathologic correlation. Radiology 1990; 176: 339–43.

123. Ellis WJ, Chetner MP, Preston SD et al. Diagnosis of prostatic carcinoma: the yield of serum prostate specific antigen, digital rectal examination and transrectal ultrasonography. J Urol 1994; 152: 1520–5.

124. Mazzucchelli R, Colanzi P, Pomante R et al. Prostate tissue and serum markers. Adv Clin Path 2000; 4: 111–20.

125. Montironi R, Mazzucchelli R, Algaba F et al. Prostate-specific antigen as a marker of prostate disease. Virch Arch 2000; 436: 297–304.

126. Thiel RP, Oesterling JE, Wojno KJ et al. Multicenter comparison of the diagnostic performance of free prostate-specific antigen. Urology 1996; 48: 45–50.

127. Aus G, Bergdahl S, Frosing R et al. Reference range of prostate-specific antigen after transurethral resection of the prostate. Urology 1996; 47: 529–31.

128. Hammerer PG, McNeal JE, Stamey TA. Correlation between serum prostate specific antigen levels and the volume of the individual glandular zones of the human prostate. J Urol 1995; 153: 111–14.

129. Lloyd SN, Collins GN, McKelvie GB et al. Predicted and actual change in serum PSA following prostatectomy for BPH. Urology 1994; 43: 472–9.

130. Carter HB, Morrell CH, Pearson JD et al. Estimation of prostatic growth using serial prostate-specific antigen measurements in men with and without prostate disease. Cancer Res 1992; 52: 3323–8.

131. Carter HB, Pearson JD, Metter EJ et al. Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. JAMA 1992; 267: 2215–20.

132. Hammerer P, Huland H. Systematic sextant biopsies in 651 patients referred for prostate evaluation. J Urol 1994; 151: 99–102.

133. Melchior SW, Brawer MK. Role of transrectal ultrasound and prostate biopsy. J Clin Ultrasound 1996; 24: 463–71.

134. Hodge KK, McNeal JE, Terris MK et al. Random systematic versus directed ultrasound guided transrectal core biopsies of the prostate. J Urol 1989; 142: 71–4.

135. Applewhite JC, Matlaga BR, McCullough DL. Results of the 5 region prostate biopsy method: the repeat biopsy population. J Urol 2002; 168: 500–3.

136. Eskew LA, Bare RL, McCullough DL. Systematic 5 region prostate biopsy is superior to sextant method for diagnosing carcinoma of the prostate. J Urol 1997; 157: 199–202.

137. Ravery V, Goldblatt L, Royer B et al. Extensive biopsy protocol improves the detection rate of prostate cancer. J Urol 2000; 164: 393–6.

138. Fleshner NE, Fair WR. Indications for transition zone biopsy in the detection of prostatic carcinoma. J Urol 1997; 157: 556–8.

139. Terris MK, Pham TQ, Issa MM et al. Routine transition zone and seminal vesicle biopsies in all patients undergoing transrectal ultrasound guided prostate biopsies are not indicated. J Urol 1997; 157: 204–6.

140. Greene DR, Wheeler TM, Egawa S et al. Relationship between clinical stage and histologic zone of origin in early prostate cancer: morphometric analysis. Br J Urol 1991; 68: 499–509.

141. McNeal JE, Price HM, Redwine EA et al. Stage A versus stage B adenocarcinoma of the prostate: morphological comparison and biological significance. J Urol 1988; 139: 61–5.

142. McNeal JE, Redwine EA, Freiha FS et al. Zonal distribution of prostatic adenocarcinoma. Correlation with histologic pattern and direction of spread. Am J Surg Pathol 1988; 12: 897–906.

143. Epstein JI, Oesterling JE, Walsh PC. The volume and anatomical location of residual tumor in radical prostatectomy specimens removed for stage A1 prostate cancer. J Urol 1988; 139: 975–9.

144. Waisman J, Adolfsson J, Lowhagen T et al. Comparison of transrectal prostate digital aspiration and ultrasound-guided core biopsies in 99 men. Urology 1991; 37: 301–7.

145. Byar DP, Mostofi FK. The Veterans Administrative Cooperative Urologic Research Groups. Carcinoma of the prostate: prognostic evaluation of certain pathologic features in 208 radical prostatectomies. Cancer 1972; 30: 5–13.

146. Mc Neal JE. Origin and development of carcinoma in the prostate. Cancer 1969; 23: 24–34.

147. Epstein JI, Walsh PC, Carmichael MJ et al. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. JAMA 1994; 271: 368–74.

148. Bostwick DG, Foster CS. Examination of radical prostatectomy specimens: therapeutic and prognostic significance. In: Foster CS, Bostwick DG, eds. Pathology of the Prostate. Philadelphia, PA: WB Saunders; 1997: 172–89.

149. Hall GS, Kramer CE, Epstein JI. Evaluation of radical prostatectomy specimens. A comparative analysis of sampling methods. Am J Surg Pathol 1992; 16: 315–24.

150. Young RH, Srigley JR, Amin MB et al. Carcinomas of the prostate gland (excluding unusual variants and secondary carcinomas). In: Young RH, Srigley JR, Amin MB, Ulbright TM, Cubilla AL, eds. Tumors of the Prostate Gland, Seminal Vesicles, Male Urethra and Penis (Fascicle 28), 3rd edn. Washington DC: Armed Forces Institute of Pathology; 2000: 111–216.

151. Bostwick DG, Grignon DJ, Hammond ME et al. Prognostic factors in prostate cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med 2000; 124: 995–1000.

152. Epstein JI. The evaluation of radical prostatectomy specimens. Therapeutic and prognostic implications. Pathol Annu 1991; 26: 159–210.

153. Renshaw AA. Correlation of gross morphologic features with histologic features in radical prostatectomy specimens. Am J Clin Pathol 1998; 110: 38–42.

154. Del Rosario AD, Bui HX, Abdulla M et al. Sulfur-rich prostatic intraluminal crystalloids: a surgical pathologic and electron probe X-ray microanalytic study. Hum Pathol 1993; 24: 1159–67.

155. Molberg KH, Mikhail A, Vuitch F. Crystalloids in metastatic prostatic adenocarcinoma. Am J Clin Pathol 1994; 101: 266–8.

156. Goldstein NS, Qian J, Bostwick DG. Mucin expression in atypical adenomatous hyperplasia of the prostate. Hum Pathol 1995; 26: 887–91.

157. Bostwick DG, Wollan P, Adlakha K. Collagenous micronodules in prostate cancer: a specific but infrequent diagnostic finding. Arch Pathol Lab Med 1995; 119: 444–7.

158. Darson MF, Pacelli A, Roche P et al. Human glandular kallikrein 2 (hK2) expression in prostatic intraepithelial neoplasia and adenocarcinoma: a novel prostate cancer marker. Urology 1997; 49: 857–62.

159. Bostwick DG. Prostate-specific antigen: current role in diagnostic pathology of prostate cancer. Am J Clin Pathol 1994; 102: 531–7.

160. Lowe FC, Trauzzi SJ. Prostatic acid phosphatase in 1993: its limited clinical utility. Urol Clin North Am 1993; 20: 589–95.

161. Foster CS, Bostwick DG, eds. Pathology of the Prostate. Philadelphia, PA: WB Saunders Company, 1998.

162. Hendrick L, Epstein JI. Use of keratin 903 as an adjunct in the diagnosis of prostate carcinoma. Am J Surg Pathol 1989; 13: 389–96.

163. Young RH, Srigley JR, Amin MB et al. Tumors of the prostate gland, seminal vesicles, male urethra and penis (Fascicle 28), 3rd edn. Armed Forces Institute of Pathology. Washington DC: 2000.

164. Oliai BR, Kahane H, Epstein JI. Can basal cells be seen in adenocarcinoma of the prostate? An immunohistochemical study using high molecular weight cytokeratin (clone 34betaE12) antibody. Am J Surg Pathol 2002; 26: 1151–60.

165. Genega EM, Hutchinson B, Reuter VE et al. Immunophenotype of high-grade prostatic adenocarcinoma and urothelial carcinoma. Mod Pathol 2000; 13: 1186–91.

166. Kaufmann O, Fietze E, Mengs J et al. Value of p63 and cytokeratin 5/6 as immunohistochemical markers for the differential diagnosis of poorly differentiated and undifferentiated carcinomas. Am J Clin Pathol 2001; 116: 823–30.

167. Xu J, Stolk JA, Zhang X et al. Identification of differentially expressed genes in human prostate cancer using subtraction and microarray. Cancer Res 2000; 60: 1677–82.

168. Beach R, Gown AM, De Peralta-Venturina MN et al. P504S immunohistochemical detection in 405 prostatic specimens including 376 18-gauge needle biopsis. Am J Surg Pathol 2002; 26: 1588–96.

169. Jiang Z, Woda BA, Rock KL et al. P504S: a new molecular marker for the detection of prostate carcinoma. Am J Surg Pathol 2001; 25: 1397–1404.

170. Zhou M, Chinnaiyan AM, Kleer CG et al. Alpha-methylacyl-CoA racemase: a novel tumor marker over-expressed in several human cancers and their precursor lesions. Am J Surg Pathol 2002; 26: 926–31.

171. Jiang Z, Wu CL, Woda BA et al. P504S/alpha-methylacyl-CoA racemase: a useful marker for diagnosis of small foci of prostatic carcinoma on needle biopsy. Am J Surg Pathol 2002; 26: 1169–74.

172. Yang XJ, Wu CL, Woda BA et al. Expression of alpha-methylacyl-CoA racemase (P504S) in atypical adenomatous hyperplasia of the prostate. Am J Surg Pathol 2002; 26: 921–5.

173. Abrahamsson PA. Neuroendocrine differentiation in prostatic carcinoma. Prostate 1999; 39: 135–48.

174. Abrahamsson PA, Wadstrom LB, Alumets J et al. Peptide-hormone- and serotonin-immunoreactive tumor cells in carcinoma of the prostate. Pathol Res Pract 1987; 82: 298–307.

175. Bonkhoff H. Neuroendocrine differentiation in human prostate cancer. Morphogenesis, proliferation and androgen receptor status. Ann Oncol 2001; 12: S141–4.

176. di Sant'Agnese PA. Neuroendocrine differentiation in carcinoma of the prostate. Diagnostic, prognostic, and therapeutic implications. Cancer 1992; 70: 254–68.

177. di Sant'Agnese PA. Neuroendocrine differentiation in prostatic carcinoma: an update on recent developments. Ann Oncol 2001; 12: S135–40.

178. di Sant'Agnese PA, Mesy Jensen KL. Neuroendocrine differentiation in prostatic carcinoma. Hum Pathol 1987; 18: 849–56.

179. Hansson J, Abrahamsson PA. Neuroendocrine pathogenesis in adenocarcinoma of the prostate. Ann Oncol 2001; 12: S145–52.

180. Helpap B, Kloppel G. Neuroendocrine carcinoma of the prostate and urinary bladder: a diagnostic and therapeutic challenge. Virch Arch 2002; 440: 241–8.

181. Helpap B, Kollermann J. Immunohistochemical analysis of the proliferative activity of neuroendocrine tumors from various organs. Are there indications for a neuroendocrine tumor–carcinoma sequence? Virch Arch 2001; 438: 86–91.

182. Ishimaru H, Kageyama Y, Hayashi T et al. Expression of matrix metalloproteinase-9 and bombesin/gastrin-releasing peptide in human prostate cancers and their lymph node metastases. Acta Oncol 2002; 41: 289–96.

183. Abdul M, Anezinis PE, Logothetis CJ et al. Growth inhibition of human prostatic carcinoma cell lines by serotonin antagonists. Anticancer Res 1994; 14: 1215–20.

184. Hansson J, Bjartell A, Gadaleanu V et al. Expression of somatostatin receptor subtypes 2 and 4 in human benign prostatic hyperplasia and prostatic cancer. Prostate 2002; 53: 50–9.

185. Sun B, Halmos G, Schally AV et al. Presence of receptors for bombesin/gastrin-releasing peptide and mRNA for three receptor subtypes in human prostate cancers. Prostate 2000; 42: 295–303.

186. Cheville JC, Tindall D, Boelter C et al. Metastatic prostate carcinoma to bone: clinical and pathologic features associated with cancer-specific survival. Cancer 2002; 95: 1028–36.

187. Ito T, Yamamoto S, Ohno Y et al. Up-regulation of neuroendocrine differentiation in prostate cancer after androgen deprivation therapy, degree and androgen independence. Oncol Rep 2001; 8: 1221–4.

188. Jiborn T, Bjartell A, Abrahamsson PA. Neuroendocrine differentiation in prostatic carcinoma during hormonal treatment. Urology 1998; 51: 585–9.

189. Krijnen JL, Bogdanowicz JF, Seldenrijk CA et al. The prognostic value of neuroendocrine differentiation in adenocarcinoma of the prostate in relation to progression of disease after endocrine therapy. J Urol 1997; 158: 171–4.

190. Mucci NR, Akdas G, Manely S et al. Neuroendocrine expression in metastatic prostate cancer: evaluation of high throughput tissue microarray to detect heterogeneous protein expression. Hum Pathol 2000; 31: 406–14.

191. Tarle M, Ahel MZ, Kovacic K. Acquired neuroendocrine-positivity during maximal androgen blockade in prostate cancer patients. Anticancer Res 2002; 22: 2525–9.

192. Berruti A, Dogliotti L, Mosca A et al. Effects of the somatostatin analog lanreotide on the circulating levels of chromogranin-A, prostate-specific antigen, and insulin-like growth factor-1 in advanced prostate cancer patients. Prostate 2001; 47: 205–11.

193. Schally AV, Comaru-Schally AM, Plonowski A et al. Peptide analogs in the therapy of prostate cancer. Prostate 2000; 45: 158–66.

194. Zaky AM, Kovacic K, Kraljic I et al. Oral estramustine therapy in serum chromogranin A-positive stage D3 prostate cancer patients. Anticancer Res 2001; 21: 1475–9.

195. Humphrey PA, Kaleem Z, Swanson PE et al. Pseudohyperplastic prostatic adenocarcinoma. Am J Surg Pathol 1998; 22: 1239–46.

196. Levi AW, Epstein JI. Pseudohyperplastic prostatic adenocarcinoma on needle biopsy and simple prostatectomy. Am J Surg Pathol 2000; 24: 1039–46.

197. Tran TT, Sengupta E, Yang XJ. Prostatic foamy gland carcinoma with aggressive behavior: clinicopathologic, immunohistochemical, and ultrastructural analysis. Am J Surg Pathol 2001; 25: 618–23.

198. Nelson RS, Epstein JI. Prostatic carcinoma with abundant xanthomatous cytoplasm. Foamy gland carcinoma. Am J Surg Pathol 1996; 20: 419–26.

199. Cina SJ, Epstein JI. Adenocarcinoma of the prostate with atrophic features. Am J Surg Pathol 1997; 21: 289–95.

200. Egan AJ, Lopez-Beltran A, Bostwick DG. Prostatic adenocarcinoma with atrophic features: malignancy mimicking a benign process. Am J Surg Pathol 1997; 21: 931–5.

201. Amin MB, Tamboli P, Varma M et al. Postatrophic hyperplasia of the prostate gland: a detailed analysis of its morphology in needle biopsy specimens. Am J Surg Pathol 1999; 23: 925–31.

202. Pacelli A, Lopez-Beltran A, Egan AJ et al. Prostatic adenocarcinoma with glomeruloid features. Hum Pathol 1998; 29: 543–6.

203. Epstein JI, Lieberman PH. Mucinous adenocarcinoma of the prostate gland. Am J Surg Pathol 1985; 9: 299–308.

204. Ro JY, Grignon DJ, Ayala AG et al. Mucinous adenocarcinoma of the prostate: histochemical and immunohistochemical studies. Hum Pathol 1990; 21: 593–600.

205. Saito S, Iwaki H. Mucin-producing carcinoma of the prostate: review of 88 cases. Urology 1999; 54: 141–4.

206. Ro JY, el Naggar A, Ayala AG et al. Signet-ring-cell carcinoma of the prostate. Electron-microscopic and immunohistochemical studies of eight cases. Am J Surg Pathol 1988; 12: 453–60.

207. Hejka AG, England DM. Signet-ring cell carcinoma of prostate. Immunohistochemical and ultrastructural study of a case. Urology 1989; 34: 155–8.

208. Uchijima Y, Ito H, Takahashi M et al. Prostate mucinous adenocarcinoma with signet-ring cell. Urology 1990; 36: 267–8.

209. Ordonez NG, Ro JY, Ayala AG. Metastatic prostatic carcinoma presenting as an oncocytic tumor. Am J Surg Pathol 1992; 16: 1007–12.

210. Pinto JA, Gonzalez JE, Granadillo MA. Primary carcinoma of the prostate with diffuse oncocytic changes. Histopathology 1994; 25: 286–8.

211. Adlakha K, Bostwick DG. Lymphoepithelioma-like carcinoma of the prostate. J Urol Pathol 1994; 2: 319–25.

212. Randolph TL, Amin MB, Ro JY, Ayala AG. Histologic variants of adenocarcinoma and other carcinomas of prostate: pathologic criteria and clinical significance. Mod Pathol 1997; 10: 612–29.

213. Bostwick DG, Kindrachuk RW, Rouse RV. Prostatic adenocarcinoma with endometrioid features. Clinical, pathologic, and ultrastructural findings. Am J Surg Pathol 1985; 9: 595–609.

214. Epstein JI, Woodruff JM. Adenocarcinoma of the prostate with endometrioid features. A light microscopic and immunohistochemical study of ten cases. Cancer 1986; 57: 111–19.

215. Green LF, Farrow GM, Ravits JM. Prostatic adenocarcinoma of ductal origin. J Urol 1979; 303–5.

216. Brinker DA, Potter SR, Epstein JI. Ductal adenocarcinoma of the prostate diagnosed on needle biopsy: correlation with clinical and radical prostatectomy findings and progression. Am J Surg Pathol 1999; 23: 1471–9.

217. Bostwick DG. Neoplasm of the prostate. In: Epstein JI, Young XJ, eds. Urologic Surgical Pathology, Urologic Surgical Pathology. St Louis, MO: Mosby; 1997; 366–8.

218. Epstein JI, Yang XJ. Prostatic duct adenocarcinoma. In: Bostwick AG, ed. Prostate Biopsy Interpretation. Philadelphia, PA: Lippincott Williams & Wilkins; 2002; 185–97.

219. Christensen WN, Steinberg G, Walsh PC et al. Prostatic duct adenocarcinoma. Findings at radical prostatectomy. Cancer 1991; 67: 2118–24.

220. Ro JY, Ayala AG, Wishnow KI et al. Prostatic duct adenocarcinoma with endometrioid features: immunohistochemical and electron microscopic study. Semin Diagn Pathol 1988; 5: 301–11.

221. Ro JY, Tetu B, Ayala AG et al. Small cell carcinoma of the prostate. II. Immunohistochemical and electron microscopic studies of 18 cases. Cancer 1987; 59: 977–82.

222. Tetu B, Ro JY, Ayala AG et al. Small cell carcinoma of the prostate. Part I. A clinicopathologic study of 20 cases. Cancer 1987; 59: 1803–9.

223. Agoff SN, Lamps LW, Philip AT et al. Thyroid transcription factor-1 is expressed in extrapulmonary small cell carcinomas but not in other extrapulmonary neuroendocrine tumors. Mod Pathol 2000; 13: 238–42.

224. Ordonez NG. Value of thyroid transcription factor-1 immunostaining in distinguishing small cell lung carcinomas from other small cell carcinomas. Am J Surg Pathol 2000; 24: 1217–23.

225. Benchekroun A, Zannoud M, Ghadouane M et al. Sarcomatoid carcinoma of the prostate. Prog Urol 2001; 11: 327–30.

226. Delahunt B, Eble JN, Nacey JN, Grebe SK. Sarcomatoid carcinoma of the prostate: progression from adenocarcinoma is associated with p53 over-expression. Anticancer Res 1999; 19: 4279–83.

227. Dundore PA, Cheville JC, Nascimento AG et al. Carcinosarcoma of the prostate. Report of 21 cases. Cancer 1995; 76: 1035–42.

228. Lopez-Beltran A, Pacelli A, Rothenberg HJ et al. Carcinosarcoma and sarcomatoid carcinoma of the bladder: clinicopathological study of 41 cases. J Urol 1998; 159: 1497–503.

229. Reuter VE. Sarcomatoid lesions of the urogenital tract. Semin Diagn Pathol 1993; 10: 188–201.

230. Shannon RL, Ro JY, Grignon DJ et al. Sarcomatoid carcinoma of the prostate. A clinicopathologic study of 12 patients. Cancer 1992; 69: 2676–82.

231. Luque Barona RJ, Gonzalez CR, Vicioso RL et al. Synchronous prostatic carcinosarcoma: report of 2 cases and review of the literature. Actas Urol Esp 2000; 24: 173–8.

232. Poblet E, Gomez-Tierno A, Alfaro L. Prostatic carcinosarcoma: a case originating in a previous ductal adenocarcinoma of the prostate. Pathol Res Pract 2000; 196: 569–72.

233. Gleason DF. Classification of prostatic carcinomas. Cancer Chemother Rep 1966; 50: 125–8.

234. Gleason DF. Histologic grading and clinical staging of prostatic carcinoma. In: Tannenbaum M, ed. Urologic Pathology: The Prostate. Philadelphia, PA: Lea and Feibiger; 1977.

235. Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histologic grading and clinical staging. J Urol 1974; 111: 58–64.

236. Bostwick DG. Gleason grading of prostatic needle biopsies. Correlation with grade in 316 matched prostatectomies. Am J Surg Pathol 1994; 18: 796–803.

237. Egevad L, Allsbrook WC Jr, Epstein JI. Current practice of Gleason grading among genitourinary pathologists. Hum Pathol 2005; 36: 5–9.

238. Epstein JI, Allsbrook WCJ, Amin MB et al. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason grading of prostatic carcinoma. Am J Surg Pathol 2005; 29: 1228–42.

239. Amin MB, Grignon DJ, Humphrey PA et al. Gleason grading of prostate cancer: a contemporary approach. Philadelphia, PA: Lippincott Williams & Wilkins; 2004.

240. Eble JN, Sauter G, Epstein JI et al. Pathology and genetics. Tumors of the urinary system and male genital organs. Lyon, France; IARC Press, 2004; 162–92.

241. Epstein JI, Amin M, Boccon-Gibod L et al. Prognostic factors and reporting of prostate carcinoma in radical prostatectomy and pelvic lymphadenectomy specimens. Scand J Urol Nephrol 2005; 216: 34–63.

242. Mazzucchelli R, Lopez-Beltran A, Scarpelli M et al. Predictive factors in prostate needle biopsy. Pathologica 2002; 94: 331–7.

243. Mazzucchelli R, Santinelli A, Lopez-Beltran A et al. Evaluation of prognostic factors in radical prostatectomy specimens with cancer. Urol Int 2002; 68: 209–15.

244. Montironi R, Mazzucchelli R, Scarpelli M et al. Gleason grading of prostate cancer in needle biopsies or radical prostatectomy specimens: contemporary approach, current clinical significance and sources of pathology discrepancies. BJU Int 2005; 95: 1146–52.

245. Montironi R, Scarpelli M, Lopez Beltran A. Carcinoma of the prostate: inherited susceptibility, somatic gene defects and androgen receptors. Virch Arch 2004; 444: 503–8.

246. Amin MB, Schultz DS, Zarbo RJ. Analysis of cribriform morphology in prostatic neoplasia using antibody to high-molecular-weight cytokeratins. Arch Pathol Lab Med 1994; 118: 260–4.

247. Augustin H, Eggert T, Wenske S et al. Comparison of accuracy between the Partin tables of 1997 and 2001 to predict final pathological stage in clinically localized prostate cancer. J Urol 2004; 171: 177–81.

248. Babaian RJ, Troncoso P, Bhadkamkar VA, Johnston DA. Analysis of clinicopathologic factors predicting outcome after radical prostatectomy. Cancer 2001; 91: 1414–22.

249. Bailar JC 3rd, Mellinger GT, Gleason DF. Survival rates of patients with prostatic cancer, tumor stage, and differentiation – preliminary report. Cancer Chemother Rep 1966; 50: 129–36.

250. Chan TY, Partin AW, Walsh PC et al. Prognostic significance of Gleason score 3+4 versus Gleason score 4+3 tumor at radical prostatectomy. Urology 2000; 56: 823–17.

251. Cheng L, Koch MO, Juliar BE et al. The combined percentage of Gleason patterns 4 and 5 is the best predictor of cancer progression after radical prostatectomy. J Clin Oncol 2005; 23: 2911–17.

252. Epstein JI. Gleason score 2–4 adenocarcinoma of the prostate on needle biopsy: a diagnosis that should not be made. Am J Surg Pathol 2000; 24: 477–8.

253. Epstein JI, Partin AW, Sauvageot J et al. Prediction of progression following radical prostatectomy. A multivariate analysis of 721 men with long-term follow-up. Am J Surg Pathol 1996; 20: 286–92.

254. Humphrey PA. Prostate Pathology. Chicago, IL: ASCP Press; 2003: 227–57.

255. Kattan MW, Eastham JA, Wheeler TM et al. Counseling men with prostate cancer: a nomogram for predicting the presence of small, moderately differentiated, confined tumors. J Urol 2003; 170: 1792–7.

256. Kunz GM Jr, Epstein JI. Should each core with prostate cancer be assigned a separate Gleason score? Hum Pathol 2003; 34: 911–14.

257. Makarov DV, Sanderson H, Partin AW et al. Gleason score 7 prostate cancer on needle biopsy: is the prognostic difference in Gleason scores 4 + 3 and 3 + 4 independent of the number of involved cores? J Urol 2002; 167: 2440–2.

258. Mosse CA, Magi-Galluzzi C, Tsuzuki T et al. The prognostic significance of tertiary Gleason pattern 5 in radical prostatectomy specimens. Am J Surg Pathol 2004; 28: 394–8.

259. Partin AW, Kattan MW, Subong EN et al. Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer. A multi-institutional update. JAMA 1997; 277: 1445–51.

260. Rubin MA, Bismar TA, Curtis S et al. Prostate needle biopsy reporting: how are the surgical members of the Society of Urologic Oncology

using pathology reports to guide treatment of prostate cancer patients? Am J Surg Pathol 2004; 28: 946–52.

261. Rubin MA, Dunn R, Kambham N et al. Should a Gleason score be assigned to a minute focus of carcinoma on prostate biopsy? Am J Surg Pathol 2000; 24: 1634–40.

262. Sakr WA, Tefilli MV, Grignon DJ et al. Gleason score 7 prostate cancer: a heterogeneous entity? Correlation with pathologic parameters and disease-free survival. Urology 2000; 56: 730–4.

263. Allsbrook WC Jr, Mangold KA, Johnson MH et al. Interobserver reproducibility of Gleason grading of prostatic carcinoma: urologic pathologists. Hum Pathol 2001; 32: 74–80.

264. Allsbrook WC Jr, Mangold KA, Johnson MH et al. Interobserver reproducibility of Gleason grading of prostatic carcinoma: general pathologist. Hum Pathol 2001; 32: 81–8.

265. Lopez-Beltran A, Qian J, Montironi R et al. Atypical adenomatous hyperplasia (adenosis) of the prostate: DNA ploidy analysis and immunophenotype. Int J Surg Pathol 2005; 13: 167–73.

266. Mills SE, Fowler JE Jr. Gleason histologic grading of prostatic carcinoma. Correlations between biopsy and prostatectomy specimens. Cancer 1986; 57: 346–9.

267. Steinberg DM, Sauvageot J, Piantadosi S et al. Correlation of prostate needle biopsy and radical prostatectomy Gleason grade in academic and community settings. Am J Surg Pathol 1997; 21: 566–76.

268. Pan CC, Potter SR, Partin AW et al. The prognostic significance of tertiary Gleason patterns of higher grade in radical prostatectomy specimens: a proposal to modify the Gleason grading system. Am J Surg Pathol 2000; 24: 563–9.

269. Grober ED, Tsihlias J, Jewett MA et al. Correlation of the primary Gleason pattern on prostate needle biopsy with clinico-pathological factors in Gleason 7 tumors. Can J Urol 2004; 11: 2157–62.

270. Mian BM, Troncoso P, Okihara K et al. Outcome of patients with Gleason score 8 or higher prostate cancer following radical prostatectomy alone. J Urol 2002; 167: 1675–80.

271. Lopez-Beltran A, Eble JN, Bostwick DG. Pleomorphic giant cell carcinoma of the prostate. Arch Pathol Lab Med 2005; 129: 683–5.

272. Montironi R, Mazzucchelli R, van der Kwast T. Morphological assessment of radical prostatectomy specimens. A protocol with clinical relevance. Virch Arch 2003; 442: 211–17.

273. Garnett JE, Oyasu R, Grayhack JT. The accuracy of diagnostic biopsy specimens in predicting tumor grades by Gleason's classification of radical prostatectomy specimens. J Urol 1984; 131: 690–3.

274. Mills SE, Fowler JE Jr. Gleason histologic grading of prostatic carcinoma. Correlation between biopsy and prostatectomy specimens. Cancer 1986; 57: 346–9.

275. Cintra ML, Billis A. Histologic grading of prostatic adenocarcinoma. Intraobserver reproducibility of the Mostofi, Gleason, and Böcking grading systems. Int Urol Nephrol 1991; 23: 449–54.

276. Özdamar SO, Sarikaya S, Yildiz L et al. Intraobsever and interobserver reproducibility of WHO and Gleason histologic grading systems in prostatic adenocarcinomas. Int Urol Nephrol 1996; 28: 73–7.

277. Bostwick DG, Foster CS, Algaba F et al. Prostate tissue factors. In: Murphy G, Denis L, Khoury S, Partin A, Fenis L, eds. Prostate Cancer. Second International Consultation on Prostate Cancer, Co-Sponsored by WHO and UICC. London: Plymbridge Distributions Ltd; 2000.

278. Montironi R, Magi Galluzzi C, Scarpelli M et al. Quantitative characterisation of the frequency and location of cell proliferation and death in prostate pathology. J Cell Biochem 1994; 19: 238–45.

279. Ferguson J, Zincke H, Ellison E et al. Decrease of prostatic intraepithelial neoplasia (PIN) following androgen deprivation therapy in patients with stage T3 carcinoma treated by radical prostatectomy. Urology 1994; 44: 91–5.

280. Vaillancourt L, Tetu B, Fradet Y et al. Effect of neoadjuvant endocrine therapy (combined androgen blockade) on normal prostate and prostatic carcinoma. J Surg Pathol 1996; 20: 86–93.

281. Montironi R, Magi Galluzzi C, Muzzonigro G et al. Effect of Combination Endocrine Therapy (LHRH agonist and flutamide) on normal prostate, Prostatic Intraepithelial Neoplasia and prostatic adenocarcinoma. J Clin Pathol 1994; 47: 906–13.

282. Montironi R, Mazzucchelli R, Marshall JR et al. Prostate cancer prevention: review of target populations, pathological biomarkers, and chemopreventive agents. J Clin Pathol 1999; 52: 793–803.

283. Armas OA, Aprikian A, Melamed J et al. Clinical and pathobiological effects of neoadjuvant total androgen ablation therapy in clinically localized prostatic carcinoma. Am J Surg Pathol 1994; 18: 979–91.

284. Magi Galluzzi C, Montironi R, Giannulis I et al. Prostatic invasive adenocarcinoma. Effect of combination endocrine therapy (LHRH agonist and flutamide) on the expression and location of Proliferating Cell Nuclear Antigen (PCNA). Path Res Pract 1993; 189: 1154–60.

285. Montironi R, Magi-Galluzzi C, Fabris G. Apoptotic bodies in prostatic intraepithelial neoplasia and prostatic adenocarcinoma following total androgen ablation. Path Res Pract 1995; 191: 873–80.

286. Murphy WM, Soloway MS, Barrows GH. Pathologic changes associated with androgen deprivation therapy for prostate cancer. Cancer 1991; 68: 821–8.

287. Reuter VE. Pathological changes in benign and malignant prostatic tissue following androgen deprivation therapy. Urology 1997; 49(Suppl 3A): 16–22.

288. Smith DM, Murphy WM. Histologic changes in prostate carcinomas treated with leuprolide (luteinizing hormone-releasing hormone effect). Distinction from poor tumor differentiation. Cancer 1994; 73: 1472–7.

289. Têtu B, Srigley JR, Boivin J-C et al. Effect of combination endocrine therapy (LHRH agonist and flutamide) on normal prostate and prostatic adenocarcinoma. Am J Surg Pathol 1991; 15: 111–20.

290. Van de Voorde WM, Elgamal AA, Van Poppel HP et al. Morphologic and immunohistochemical changes in prostate cancer after preoperative hormonal therapy. Cancer 1994; 74: 3164–75.

291. Akakura K, Bruchovsky N, Goldenberg N et al. Effects of intermittent androgen suppression on androgen-dependent tumors. Cancer 1993; 71: 2782–90.

292. Schulman CC, Wildschutz T, Zlotta AR. Neoadjuvant hormonal treatment prior to radical prostatectomy: facts and questions. Eur Urol 1997; 32: 41–7.

293. Gleave ME, Goldenberg SL, Jones EC et al. Optimal duration of neoadjuvant androgen withdrawal therapy before radical prostatectomy in clinically confined prostate cancer. Sem Urol Oncol 1996; 14(Suppl 2): 39–47.

294. Bazinet M, Zheng W, Begin LR et al. Morphologic changes induced by neoadjuvant androgen ablation may result in underdetection of positive surgical margins and capsular involvement by prostatic adenocarcinoma. Urology 1997; 49: 721–5.

295. Gould VE, Doljanskaia V, Gooch GT et al. Stability of the glycoprotein A-80 in prostatic carcinoma subsequent to androgen deprivation therapy. Am J Surg Pathol 1997; 21: 319–26.

296. Schulman CC, Sassine AM. Neoadjuvant hormonal deprivation before radical prostatectomy. Eur Urol 1993; 24: 450–5.

297. Montironi R, Bartels PH, Thompson D et al. Androgen-deprived prostate adenocarcinoma: evaluation of treatment-related changes versus no distinctive treatment effect with a Bayesian Belief network. Eur Urol 1996; 30: 307–15.

298. Abbas F, Scardino PT. Why neoadjuvant androgen deprivation prior to radical prostatectomy is unnecessary. Urol Clin North Am 1996; 23: 587–604.

299. Cheng L, Cheville JC, Pisansky TM et al. Prevalence and distribution of prostatic intraepithelial neoplasia in salvage radical prostatectomy specimens after radiation therapy. Am J Surg Pathol 1999; 23: 803–8.

300. Akakura K, Bruchovsky N, Goldemberg N et al. Effects of intermittent androgen suppression on androgen-dependent tumors. Apoptosis and serum prostate-specific antigen. Cancer 1993; 71: 2782–90.

301. Wheeler TM. Influence of irradiation and androgen ablation on prostatic intraepithelial neoplasia. Eur Urol 1996; 30: 261–4.

302. Dhom G, Degro S. Therapy of prostatic cancer and histopathologic follow-up. Prostate 1982; 3: 531–42.

303. Gaudin PB. Histopathologic effects of radiation and hormonal therapies on benign and malignant prostate tissue. J Urol Pathol 1998; 8: 55–67.

304. Helpap B. Treated prostatic carcinoma. Histological, immunohistochemical and cell kinetic studies. Appl Pathol 1985; 3: 230–41.

305. Helpap B. Fundamentals on the pathology of the prostatic carcinoma after brachytherapy. World J Urol 2002; 20: 207–12.

306. Helpap B, Koch V. Histologic and immunohistochemical findings of prostatic carcinoma after external or interstitial radiotherapy. J Cancer Res Clin Oncol 1991; 117: 608–14.

307. Herr HW, Whitmore WF Jr. Significance of prostatic biopsies after radiation therapy for carcinoma of the prostate. Prostate 1982; 3: 339–50.

308. Lytton B, Collins JT, Weiss RM et al. Results of biopsy after early stage prostatic cancer treatment by implantation of 125I seeds. J Urol 1979; 121: 306–9.

309. Crook J, Malone S, Perry G et al. Postradiotherapy prostate biopsies: what do they really mean? Results for 498 patients. Int J Radiat Oncol Biol Phys 2000; 48: 355–67.

310. Bostwick DG, Adolfsson J, Burke HB et al. Epidemiology and statistical methods in prediction of patient outcome. Scand J Urol Nephrol 2005; 216: 94–110.

311. Montironi R, Mazzucchelli R, Lopez-Beltran A et al. Prostate carcinoma II. Prognostic factors in prostate needle biopsies. BJU Int 2006; 97: 492–7.

312. Freedland SJ, Aronson WJ, Terris MK et al. The percentage of prostate needle biopsy cores with carcinoma from the more involved side of the biopsy as a predictor of prostate specific antigen recurrence after radical prostatectomy: results from the Shared Equal Access Regional Cancer Hospital (SEARCH) database. Cancer 2003; 98: 2344–50.

313. Freedland SJ, Csathy GS, Dorey F et al. Percent prostate needle biopsy tissue with cancer is more predictive of biochemical failure or adverse pathology after radical prostatectomy than prostate specific antigen or Gleason score. J Urol 2002; 167: 516–20.

314. Gancarczyk KJ, Wu H, McLeod DG et al. Using the percentage of biopsy cores positive for cancer, pretreatment PSA, and highest biopsy Gleason sum to predict pathologic stage after radical prostatectomy: the Center for Prostate Disease Research nomograms. Urology 2003; 61: 589–95.

315. Kronz JD, Allan CH, Shaikh AA et al. Predicting cancer following a diagnosis of high-grade prostatic intraepithelial neoplasia on needle biopsy: data on men with more than one follow-up biopsy. Am J Surg Pathol 2001; 25: 1079–85.

316. Freedland SJ, Aronson W, Presti JC Jr et al. The SEARCH Database Study Group. Percent of prostate needle biopsy cores with cancer is significant independent predictor of prostate specific antigen recurrence following radical prostatectomy: results from SEARCH database. J Urol 2003; 169: 2136–41.

317. Kestin LL, Goldstein NS, Vicini FA et al. Percentage of positive biopsy cores as predictor of clinical outcome in prostate cancer treated with radiotherapy. J Urol 2002; 168: 1994–9.

318. Lewis JS Jr, Vollmer RT, Humphrey PA. Carcinoma extent in prostate needle biopsy tissue in the prediction of whole gland tumor volume in a screening population. Am J Clin Pathol 2002; 118: 442–50.

319. Epstein JI. Diagnosis and reporting of limited adenocarcinoma of the prostate on needle biopsy. Mod Pathol 2004; 17: 307–15.

320. Thorson P, Vollmer RT, Arcangeli C et al. Minimal carcinoma in prostate needle biopsy specimens: diagnostic features and radical prostatectomy follow-up. Mod Pathol 1998; 11: 543–51.

321. Cohen RJ, Stables S. Intra-prostatic fat. Hum Pathol 1998; 29: 424–5.

322. Maru N, Ohori M, Kattan MW et al. Prognostic significance of the diameter of perineural invasion in radical prostatectomy specimens. Hum Pathol 2001; 32: 828–33.

323. Anderson PR, Hanlon AL, Patchefsky A et al. Perineural invasion and Gleason 7–10 tumors predict increased failure in prostate cancer patients with pretreatment PSA <10 ng/ml treated with conformal external beam radiation therapy. Int J Radiat Oncol Biol Phys 1998; 41: 1087–92.

324. Quinn DI, Henshall SM, Brenner PC et al. Prognostic significance of preoperative factors in localized prostate carcinoma treated with radical prostatectomy: importance of percentage of biopsies that contain tumor and the presence of biopsy perineural invasion. Cancer 2003; 97: 1884–93.

325. Vargas SO, Jiroutek M, Welch WR et al. Perineural invasion in prostate needle biopsy specimens. Correlation with extraprostatic extension at resection. Am J Clin Pathol 1999; 111: 223–8.

326. Sebo TJ, Cheville JC, Riehle DL et al. Predicting prostate carcinoma volume and stage at radical prostatectomy by assessing needle biopsy specimens for percent surface area and cores positive for carcinoma, perineural invasion, Gleason score, DNA ploidy and proliferation, and preoperative serum prostate specific antigen: a report of 454 cases. Cancer 2001; 91: 2196–204.

327. Holmes GF, Walsh PC, Pound CR et al. Excision of the neurovascular bundle at radical prostatectomy in cases with perineural invasion on needle biopsy. Urology 1999; 53: 752–6.

328. Beard CJ, Chen MH, Cote K et al. Perineural invasion is associated with increased relapse after external beam radiotherapy for men with low-risk prostate cancer and may be a marker for occult, high-grade cancer. Int J Radiat Oncol Biol Phys 2004; 58: 19–24.

329. Salomao DR, Graham SD, Bostwick DG. Microvascular invasion in prostate cancer correlates with pathologic stage. Arch Pathol Lab Med 1995; 119: 1050–4.

330. Ito K, Nakashima J, Mukai M et al. Prognostic implication of microvascular invasion in biochemical failure in patients treated with radical prostatectomy. Urol Int 2003; 70: 297–302.

331. Shariat SF, Khoddami SM, Saboorian H et al. Lymphovascular invasion is a pathological feature of biologically aggressive disease in patients treated with radical prostatectomy. J Urol 2004; 171: 1122–7.

332. Isaacs JT. Molecular markers for prostate cancer metastases: developing diagnostic methods for predicting aggressiveness of prostate cancer. Am J Pathol 1997; 150: 1511–21.

333. Schalken JA, Bergh A, Bono A et al. Molecular prostate cancer pathology: current issues and achievements. Scand J Urol Nephrol 2005; 216: 82–93.

334. Jones EC, McNeal J, Bruchovsky N et al. DNA content in prostatic adenocarcinoma: a flow cytometry study of the predictive value of aneuploidy for tumor volume, percentage Gleason grade 4 and 5, and lymph node metastases. Cancer 1990; 66: 752–7.

335. Tribukait B. Nuclear deoxyribonucleic acid determination in patients with prostate carcinoma: clinical research and application. Eur Urol 1993; 23: 64–76.

336. Takai K, Goellner JR, Katzmann JA et al. Static image and flow DNA cytometry of prostatic adenocarcinoma: studies of needle biopsy and radical prostatectomy specimens. J Urol Pathol 1994; 2: 39–48.

337. Shankey TV, Kallioniemi OP, Koslowski JM et al. Consensus review of the clinical utility of DNA content cytometry in prostate cancer. Cytometry 1993; 14: 497–500.

338. Montironi R, Magi-Galluzzi C, Diamanti L et al. Prostatic intraepithelial neoplasia: qualitative and quantitative analysis of the blood capillary architecture on thin tissue sections. Pathol Res Pract 1993; 189: 542–8.

339. Bostwick DG, Pacelli A, Lopez-Beltran A. Molecular biology of prostatic intraepithelial neoplasia. Prostate 1996; 29: 117–34.

340. ftp://ftp.cap.org/cancerprotocols/prostate03_p.doc

341. Gleason DF. Histologic grading of prostate cancer: a perspective. Hum Pathol 1992; 23: 273–9.

342. Fleming ID, Cooper JS, Henson DE et al, eds. AJCC Manual for Staging of Cancer, 5th edn. Philadelphia, PA: Lippincott Raven; 1997.

343. Sobin LH, Wittekind C, eds. TNM Classification of Malignant Tumors: International Union Against Cancer, 6th edn. New York: Wiley-Liss, 2002.

344. Grignon DJ, Sakr WA. Pathologic staging of prostate carcinoma. What are the issues. Cancer 1996; 78: 337–40.

345. Bostwick DG, Montironi R. Evaluating radical prostatectomy specimens: therapeutic and prognostic importance. Virch Arch 1997; 430: 1–16.

346. Epstein JI, Partin AW, Potter SR et al. Adenocarcinoma of the prostate invading the seminal vesicle: prognostic stratification based on pathologic parameters. Urology 2000; 56: 283–8.

347. Ohori M, Scardino PT, Lapin SL et al. The mechanisms and prognostic significance of seminal vesicle involvement by prostate cancer. Am J Surg Pathol 1993; 17: 1252–61.

348. Catalona WJ, Smith DS. Cancer recurrence and survival rates after anatomic radical retropubic prostatectomy for prostate cancer: intermediate-term results. J Urol 1998; 160: 2428–34.

349. D'Amico AV, Whittington R, Malkowicz SB et al. A multivariate analysis of clinical and pathological factors that predict for prostate specific antigen failure after radical prostatectomy for prostate cancer. J Urol 1995; 154: 131–8.

350. Debras B, Guillonneau B, Bougaran J et al. Prognostic significance of seminal vesicle invasion on the radical prostatectomy specimen. Rationale for seminal vesicle biopsies. Eur Urol 1998; 33: 271–7.

351. Tefilli MV, Gheiler EL, Tiguert R et al. Prognostic indicators in patients with seminal vesicle involvement following radical prostatectomy for clinically localized prostate cancer. J Urol 1998; 160: 802–6.

352. Sakr WA, Wheeler TM, Blute M et al. Staging and reporting of prostate cancer; sampling of the radical prostatectomy specimen. Cancer 1996; 78: 366–9.

353. Hoedemaeker RF, Ruijter ETG, Ruizeveld-de Winter JA et al. Processing radical prostatectomy specimens. A comprehensive and standardized protocol. J Urol Pathol 1998; 9: 211–22.

354. Hoedemaeker RF, Vis AN, Van der Kwast TH. Staging prostate cancer. Microsc Res Tech 2000; 51: 423–9.

355. True LD. Surgical pathology examination of the prostate gland. Practice survey by American Society of Clinical Pathologists. Am J Clin Pathol 1994; 102: 572–9.

356. Amin MB, Grignon D, Bostwick D et al. Recommendations for reporting resected prostatic carcinomas with commentary. Pathology Case Reviews 1998; 3: 223–32.

357. Wittekind C, Henson DE, Hutter RVP et al, eds. TNM Supplement. A Commentary on Uniform Use, 2nd edn. New York: Wiley-Liss, 2001.

358. Lichtenstein P, Holm NV, Verkasalo PK et al. Environmental and heritable factors in the causation of cancer – analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 2000; 343: 78–85.

359. Tavtigian SV, Simard J, Teng DH et al. A candidate prostate cancer susceptibility gene at chromosome 17p. Nat Genet 2001; 27: 172–80.

360. Montironi R, Mazzucchelli R, Scarpelli M. Molecular techniques and prostate cancer diagnostic. Eur Urol 2003; 44: 390–400.

361. Cunningham JM, McDonnell SK, Marks A et al. Genome linkage screen for prostate cancer susceptibility loci: results from the Mayo Clinic Familial Prostate Cancer Study. Prostate 2003; 57: 335–46.

362. Nupponen NN, Wallen MJ, Ponciano D et al. Mutational analysis of susceptibility genes RNASEL/HPC1, ELAC2/HPC2, and MSR1 in sporadic prostate cancer. Genes Chromosomes Cancer 2004; 39: 119–25.

363. Wiklund F, Jonsson BA, Goransson I et al. Linkage analysis of prostate cancer susceptibility: confirmation of linkage at 8p22-23. Hum Genet 2003; 112: 414–8.

364. Xu J, Zheng SL, Komiya A et al. Germline mutations and sequence variants of the macrophage scavenger receptor 1 gene are associated with prostate cancer risk. Nat Genet 2002; 32: 321–5.

365. Seppala EH, Ikonen T, Mononen N et al. CHEK2 variants associate with hereditary prostate cancer. Br J Cancer 2003; 89: 1966–70.

366. Simard J, Dumont M, Labuda D et al. Prostate cancer susceptibility genes: lessons learned and challenges posed. Endocr Relat Cancer 2003; 10: 225–59.

367. Bova GS, Partin AW, Isaacs SD et al. Biological aggressiveness of hereditary prostate cancer: long-term evaluation following radical prostatectomy. J Urol 1998; 160: 660–3.

368. Yong EL, Lim J, Qi W et al. Molecular basis of androgen receptor diseases. Ann Med 2000; 32: 15–22.

369. Gelmann EP. Molecular biology of the androgen receptor. J Clin Oncol 2002; 20: 3001–15.

370. Giovannucci E, Stampfer MJ, Krithivas K et al. The CAG repeat within the androgen receptor gene and its relationship to prostate cancer. Proc Natl Acad Sci USA 1997; 94: 3320–3.

371. Schoenberg MP, Hakimi JM, Wang S et al. Microsatellite mutation (CAG24 ➔18) in the androgen receptor gene in human prostate cancer. Biochem Biophys Res Commun 1994; 198: 74–80.

372. Trapman J, Cleutjens KB. Androgen-regulated gene expression in prostate cancer. Semin Cancer Biol 1997; 8: 29–36.

373. Nam RK, Zhang WW, Trachtenberg J et al. Comprehensive assessment of candidate genes and serological markers for the detection of prostate cancer. Cancer Epidemiol Biomarkers Prev 2003; 12: 1429–37.

374. Ntais C, Polycarpou A, Ioannidis JP. Vitamin D receptor gene polymorphisms and risk of prostate cancer: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2003; 12: 1395–1402.

375. Artandi SE, Chang S, Lee SL et al. Telomere dysfunction promotes non-reciprocal translocations and epithelial cancers in mice. Nature 2000; 406: 641–5.

376. Blasco MA, Lee HW, Hande MP et al. Telomere shortening and tumor formation by mouse cells lacking telomerase RNA. Cell 1997; 91: 25–34.

377. Sommerfeld HJ, Meeker AK, Piatyszek MA et al. Telomerase activity: a prevalent marker of malignant human prostate tissue. Cancer Res 1996; 56: 218–22.

378. Latil A, Lidereau R. Genetic aspects of prostate cancer. Virch Arch 1998; 32: 389–406.

379. Meeker AK, Hicks JL, Platz EA et al. Telomere shortening is an early somatic DNA alteration in human prostate tumorigenesis. Cancer Res 2002; 62: 6405–9.

380. Li J, Yen C, Liaw D et al. PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer. Science 1997; 275: 1943–7.

381. Steck PA, Pershouse MA, Jasser SA et al. Identification of a candidate tumor suppressor gene, MMAC1, at chromosome 10q23.3 that is mutated in multiple advanced cancers. Nat Genet 1997; 15: 356–62.

382. Wu X, Senechal K, Neshat MS et al. The PTEN/MMAC1 tumor suppressor phosphatase functions as a negative regulator of the phosphoinositide 3-kinase/Akt pathway. Proc Natl Acad Sci USA 1998; 95: 15587–91.

383. Cordon-Cardo C, Koff A, Drobnjak M et al. Distinct altered patterns of p27[kip1] gene expression in benign prostatic hyperplasia and prostatic carcinoma. J Natl Cancer Inst 1998; 90: 1284–91.

384. Guo Y, Sklar GN, Borkowski A et al. Loss of the cyclin-dependent kinase inhibitor p27(Kip1) protein in human prostate cancer correlates with tumor grade. Clin Cancer Res 1997; 3: 2269–74.

385. Yang RM, Naitoh J, Murphy M et al. Low p27 expression predicts poor disease-free survival in patients with prostate cancer. J Urol 1998; 159: 941–5.

386. Dreher T, Zentgraf H, Abel U et al. Reduction of PTEN and p27[kip1] expression correlates with tumor grade in prostate cancer. Virch Arch 2004; 444: 509–17.

387. Ferdinandusse S, Denis S, IJlst L et al. Subcellular localization and physiological role of alpha-methylacyl-CoA racemase. J Lipid Res 2000; 41: 1890–6.

388. Kotti TJ, Savolainen K, Helander HM et al. In mouse alpha-methylacyl-CoA racemase, the same gene product is simultaneously located in mitochondria and peroxisomes. J Biol Chem 2000; 275: 20887–95.

389. Luo J, Zha S, Gage WR et al. Alpha-methylacyl-CoA racemase: a new molecular marker for prostate cancer. Cancer Res 2002; 62: 2220–6.

390. Rubin MA, Zhou M, Dhanasekaran SM et al. Alfa-methylacyl coenzyme A racemase as a tissue biomarker for prostate cancer. JAMA 2002; 287: 1662–70.

391. Lee WH, Morton RA, Epstein JI et al. Cytidine methylation of regulatory sequences near the pi-class glutathione S-transferase gene accompanies human prostatic carcinogenesis. Proc Natl Acad Sci USA 1994; 91: 11733–7.

392. Lin X, Tascilar M, Lee WH et al. GSTP1 CpG island hypermethylation is responsible for the absence of GSTP1 expression in human prostate cancer cells. Am J Pathol 2001; 159: 1815–26.

393. Zitzelsberger H, Engert D, Walch A et al. Chromosomal changes during development and progression of prostate adenocarcinoma. Br J Cancer 2001; 84: 202–8.

394. Otto T, Rembrink K, Goepel M et al. E-cadherin: a marker for differentiation and invasiveness in prostatic carcinoma. Urol Res 1993; 21: 359–62.

395. Umbas R, Schalken JA, Aalders TW et al. Expression of the cellular adhesion molecule E-cadherin is reduced or absent in high-grade prostate cancer. Cancer Res 1992; 52: 5104–9.

396. Grossmann ME, Huang H, Tindall DJ. Androgen receptor signaling in androgen-refractory prostate cancer. J Natl Cancer Inst 2001; 93: 1687–97.

397. Nupponen NN, Kakkola L, Koivisto P et al. Genetic alterations in hormone-refractory recurrent prostate carcinomas. Am J Pathol 1998; 153: 141–8.

398. Varambally S, Dhanasekaran SM, Zhou M et al. The polycomb group protein EZH2 is involved in progression of prostate cancer. Nature 2002; 419: 572–3.

399. Gelmann EP. Molecular biology of the androgen receptor. J Clin Oncol 2002; 20: 3001–15.

400. Skacel M, Ormsby AH, Pettay JD et al. Aneusomy of chromosomes 7,8 and 17 and amplification of HER-2/neu and epidermal growth factor receptor in Gleason score 7 prostate carcinoma: a differential fluorescent in situ hybridization study of Gleason pattern 3 and 4 using tissue microarray. Hum Pathol 2001; 32: 1392–7.

401. Ross RK, Pike MC, Coetzee GA et al. Androgen metabolism and prostate cancer: establishing a model of genetic susceptibility. Cancer Res 1998; 58: 4497–504.

402. Devaraj LT, Bostwick DG. Atypical basal cell hyperplasia of the prostate. Immunophenotypic profile and proposed classification of basal cell proliferations. Am J Surg Pathol 1993; 17: 645–59.

403. Epstein JI, Armas OA. Atypical basal cell hyperplasia of the prostate. Am J Surg Pathol 1992; 16: 1205–14.

404. Sesterhenn I, Mostofi FK. Basal cell hyperplasia and basal cell carcinoma. Lab Invest 1987; 56: 71A.

405. Rioux-Leclercq NC, Epstein JI. Unusual morphologic patterns of basal cell hyperplasia of the prostate. Am J Surg Pathol 2002; 26: 237–43.

406. Yang XJ, McEntee M, Epstein JI. Distinction of basaloid carcinoma of the prostate from benign basal cell lesions by using immunohistochemistry for Bcl-2 and Ki-67. Hum Pathol 1998; 28: 1447–50.

407. Van De Voorde W, Baldewijns M, Lauweryns J. Florid basal cell hyperplasia of the prostate. Histopathology 1994; 24: 341–8.

408. Yang XJ, Tretiakova MS, Sengupta E et al. Florid basal cell hyperplasia of the prostate: a histological, ultrastructural, and immunohistochemical analysis. Hum Pathol 2003; 34: 462–70.

409. Hosler GA, Epstein JI. Basal cell hyperplasia: an unusual diagnostic dilemma on prostate needle biopsies. Mod Pathol 2004; 17: 158A.

410. Humphrey PA. Basaloid and adenoid cystic carcinomas. In: PA Humphrey ed. Prostate Pathology. Chicago, IL: ASCP Press; 2003; 408–9.

411. Mastropasqua MG, Pruneri G, Renne G et al. Basaloid cell carcinoma of the prostate. Case report and review of the literature. Virch Arch 2003; 443: 787–91.

412. McEntee MF, Epstein JI, Syring R et al. Characterization of prostatic basal cell hyperplasia and neoplasia in aged macaques: comparative pathology in human and nonhuman primates. Prostate 1996; 29: 51–9.

413. Grignon DJ, Ro JY, Ordonez NG et al. Basal cell hyperplasia, adenoid basal cell tumor, and adenoid cystic carcinoma of the prostate gland: an immunohistochemical study. Hum Pathol 1988; 19: 1425–33.

414. Reed RJ. Consultation case: prostate (prostatectomy) – adenoid basal-cell tumor-multifocal basal cell hyperplasia. Am J Surg Pathol 1984; 8: 699–704.

415. Denholm SW, Webb JN, Howard GCW et al. Basaloid carcinoma of the prostate gland: histogenesis and review of the literature. Histopathology 1992; 20: 151–5.

416. Young RH, Frierson HF, Mills SE et al. Adenoid cystic-like tumor of the prostate gland. A report of two cases and review of the literature on 'adenoid cystic carcinoma' of the prostate. Am J Clin Pathol 1988; 89: 49–56.

417. Iczkowski KA, Ferguson KL, Grier DD et al. Adenoid cystic/basal cell carcinoma of the prostate. Clinicopathologic findings in 19 cases. Am J Surg Pathol 2003; 27: 1523–9.

418. Greene LF, Mulcahy JJ, Warren MM et al. Primary transitional cell carcinoma of the prostate. J Urol 1973; 110: 235–7.

419. Greene LF, O'Dea MJ, Dockerty MB. Primary transitional cell carcinoma of the prostate. J Urol 1976; 116: 761–3.

420. Mahadevia PS, Koss LG, Tar IJ. Prostatic involvement in bladder cancer. Prostate mapping in 20 cystoprostatectomy specimens. Cancer 1986; 58: 2096–102.

421. Nixon RG, Chang SS, Lafleur BJ et al. Carcinoma in situ and tumor multifocality predict the risk of prostatic urethral involvement at radical cystectomy in men with transitional cell carcinoma of the bladder. J Urol 2002; 167: 502–5.

422. Wood DP Jr, Montie JE, Pontes JE et al. Transitional cell carcinoma of the prostate in cystoprostatectomy specimens removed for bladder cancer. J Urol 1989; 141: 346–9.

423. Oliai BR, Kahane H, Epstein JI. A clinicopathologic analysis of urothelial carcinomas diagnosed on prostate needle biopsy. Am J Surg Pathol 2001; 25: 794–801.

424. Sawczuk I, Tannenbaum M, Olsson CA et al. Primary transitional cell carcinoma of prostatic periurethral ducts. Urology 1985; 25: 339–43.

425. Young R.H., Srigley JR, Amin MB et al. Tumors of the Prostate Gland, Seminal Vesicles, Male Urethra and Penis (Fascicle 28), 3rd edn. Washington DC: Armed Forces Institute of Pathology; 2000; 242–7.

426. Takashi M, Sakata T, Nagai T et al. Primary transitional cell carcinoma of prostate: case with lymph node metastasis eradicated by neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) therapy. Urology 1990; 96–8.

427. Greene FL, Page DL, Fleming ID et al. American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 6th edn. New York: Springer-Verlag; 2002.

428. Cheville JC, Dundore PA, Bostwick DG et al. Transitional cell carcinoma of the prostate: clinicopathologic study of 50 cases. Cancer 1998; 82: 703–7.

429. Bodner DR, Cohen JK, Resnick MI. Primary transitional cell carcinoma of the prostate. J Urol 1986; 92: 121–2.

430. Laplante M, Brice M. The upper limits of hopeful application of radical cystectomy for vesical carcinoma: does nodal metastasis always indicate incurability? J Urol 1973; 109: 261–4.

431. Dhom G. Histopathology of prostate carcinoma. Diagnosis and differential diagnosis. Pathol Res Pract 1985; 179: 277–303.

432. Gray GF Jr, Marshall VF. Squamous carcinoma of the prostate. J Urol 1975; 113: 736–8.

433. Bassler TJ Jr, Orozco R, Bassler IC et al. Adenosquamous carcinoma of the prostate: case report with DNA analysis, immunohistochemistry, and literature review. Urology 1999; 53: 832–4.

434. Mott LJ. Squamous cell carcinoma of the prostate: report of 2 cases and review of the literature. J Urol 1979; 121: 833–5.

435. Nabi G, Ansari MS, Singh I et al. Primary squamous cell carcinoma of the prostate: a rare clinicopathological entity. Report of 2 cases and review of literature. Urol Int 2001; 66: 216–9.

436. Accetta PA, Gardner WA Jr. Adenosquamous carcinoma of prostate. Urology 1983; 22: 73–5.

437. Ishigooka M, Yaguchi H, Tomaru M et al. Mixed prostatic carcinoma containing malignant squamous element. Reports of two cases. Scand J Urol Nephrol 1994; 28: 425–7.

438. Gattuso P, Carson HJ, Candel A et al. Adenosquamous carcinoma of the prostate. Hum Pathol 1995; 26: 123–6.

439. Tran KP, Epstein JI. Mucinous adenocarcinoma of urinary bladder type arising from the prostatic urethra. Distinction from mucinous adenocarcinoma of the prostate. Am J Surg Pathol 1996; 20: 1346–50.

440. Srigley JR, Grignon DJ, Young RH. The distinction between pure carcinoid tumor and carcinoid-like adenocarcinoma of the prostate. Mod Pathol 2002; 15: 182A-183A.

441. Tash JA, Reuter V, Russo P. Metastatic carcinoid tumor of the prostate. J Urol 2002; 167: 2526–7.

442. Têtu B, Ro JY, Ayala AG et al. Atypical spindle cell lesions of the prostate. Semin Diagn Pathol 1988; 5: 284–93.

443. Ro JY, El-Naggar AK, Amin MB et al. Pseudosarcomatous fibromyxoid tumor of the urinary bladder and prostate. Hum Pathol 1993; 24: 1203–10.

444. Young RH, Scully RE. Pseudosarcomatous lesions of the urinary bladder, prostate gland and urethra. Arch Pathol Lab Med 1987; 111: 354–8.

445. Young RH, Srigley JR, Amin MB et al. Tumors of the Prostate Gland, Seminal Vesicles, Male Urethra and Penis (Fascicle 28). Atlas of Tumor Pathology 3rd edn. Washington DC: Armed Forces Institute of Pathology; 2000; 257–88.

446. Waring PM, Newland RC. Prostatic embryonal rhabdomyosarcoma in adults. A clinicopathologic review. Cancer 1992; 69: 755–62.

447. Fain JS, Cosnow I, King BF et al. Cystosarcoma phyllodes of the seminal vesicle. Cancer 1993; 71: 2055–61.

448. Young RH, Srigley JR, Amin MB et al. Tumors of the Prostate Gland, Seminal Vesicles, Male Urethra and Penis. Atlas of Tumor Pathology 3rd edn., Washington DC: Armed Forces Institute of Pathology; 2000; 289–344.

449. Gaudin PB, Rosai J, Epstein JI. Sarcomas and related proliferative lesions of specialized prostatic stroma. Am J Surg Pathol 1998; 22: 148–62.

450. Bain GO, Danyluk JM, Shnitka TK et al. Malignant fibrous histiocytoma of prostate gland. Urology 1985; 26: 89–91.

451. Chin W, Fay R, Ortega P. Malignant fibrous histiocytoma of prostate. Urology 1986; 27: 363–5.

452. Kulmala RV, Seppanen JH, Vaajalahti PJ et al. Malignant fibrous histiocytoma of the prostate. Case report. Scand J Urol Nephrol 1994; 28: 429–31.

453. Miro AG, De Seta L, Lizza N et al. Malignant fibrous histiocytoma after radiation therapy for prostate cancer: case report. J Chemother 1997; 9: 162.

454. Sexton WJ, Lance RE, Reyes AO et al. Adult prostate sarcoma: the M. D. Anderson Cancer Center Experience. J Urol 2001; 166: 521–5.

455. Smith DM, Manivel C, Kapps D, Uecker J. Angiosarcoma of the prostate: report of 2 cases and review of the literature. J Urol 1986; 135: 382–4.

456. Algaba F, Sole-Balcells FJ. Carcinosarcoma of the prostate. Immunophenotype, morphologic course and clinico-pathologic differential diagnosis. Arch Esp Urol 1992; 45: 779–82.

457. Nishiyama T, Ikarashi T, Terunuma M et al. Osteogenic sarcoma of the prostate. Int J Urol 2001; 8: 199–201.

458. Dogra PN, Aron M, Rajeev TP et al. Primary chondrosarcoma of the prostate. BJU Int 1999; 83: 150–1.

459. Rames RA, Smith MT. Malignant peripheral nerve sheath tumor of the prostate: a rare manifestion of neurofibromatosis type 1. J Urol 1999; 162: 165–6.

460. Iwasaki H, Ishiguro M, Ohjimi Y et al. Synovial sarcoma of the prostate with t(X; 18)(p11.2;q11.2). Am J Surg Pathol 1999; 23: 220–6.

461. Kirsch AJ, Newhouse J, Hibshoosh H et al. Giant multilocular cystadenoma of the prostate. Urology 1996; 48: 303–5.

462. Maluf HM, King ME, DeLuca FR et al. Giant multilocular prostatic cystadenoma: a distinctive lesion of the retroperitoneum in men. A report of two cases. Am J Surg Pathol 1991; 15: 131–5.

463. Casiraghi O, Martinez-Madrigal F, Mostofi FK et al. Primary prostatic Wilms' tumor. Am J Surg Pathol 1991; 15: 885–90.

464. Ekfors TO, Aho HJ, Kekomaki M. Malignant rhabdoid tumor of the prostatic region. Immunohistologic and ultrastructural evidence for epithelial origin. Virch Arch A Pathol Anat Histopathol 1985; 406: 381–8.

465. Dow JA, Young JD Jr. Mesonephric adenocarcinoma of the bladder. J Urol 1968; 100: 466–9.

466. Pan CC, Chiang H, Chang YH et al. Tubulocystic clear cell adenocarcinoma arising within the prostate. Am J Surg Pathol 2000; 24: 1433–6.

467. Stein BS, Kendall AR. Malignant melanoma of the genitourinary tract. J Urol 1984; 132: 859–68.

468. Dennis PJ, Lewandowski AE, Rohner TJ Jr et al. Pheochromocytoma of the prostate: an unusual location. J Urol 1989; 141: 130–2.

469. Voges GE, Wippermann F, Duber C et al. Pheochromocytoma of the prostate in the pediatric age group: the prostate – an unusual location. J Urol 1990; 144: 1219–21.

470. Lack EE. Tumors of the Adrenal Gland and Extra-adrenal Paraganglia, 3rd edn. Washington DC: Armed Forces Institute of Pathology; 1997.

471. Bates AW, Baithun SI. Secondary solid neoplasms of the prostate: a clinico-pathological series of 51 cases. Virch Arch 2002; 440: 392–6.

472. Zein TA, Huben R, Lane W et al. Secondary tumors of the prostate. J Urol 1985; 133: 615–6.

473. Viadana E, Bross ID, Pickren JW. An autopsy study of the metastatic patterns of human leukemias. Oncology 1978; 35: 87–96.

474. Bostwick DG, Iczkowski KA, Amin MB et al. Malignant lymphoma involving the prostate: report of 62 cases. Cancer 1998; 83: 732–8.

475. Jhavar S, Agarwal JP, Naresh KN et al. Primary extranodal mucosa associated lymphoid tissue (MALT) lymphoma of the prostate. Leuk Lymphoma 2001; 41: 445–9.

476. Kao J, Upton M, Zhang P et al. Individual prostate biopsy core embedding facilitates maximal tissue representation. J Urol 2002; 168: 496–9.

477. Green R, Epstein JI. Use of intervening unstained slides for immunohistochemical stains for high molecular weight cytokeratin on prostate needle biopsies. Am J Surg Pathol 1999; 23: 567–70.

478. Naya Y, Slaton JW, Troncoso P et al. Tumor length and location of cancer on biopsy predict for side specific extraprostatic cancer extension. J Urol 2004; 171: 1093–7.

479. Zhou M, Epstein JI. The reporting of prostate cancer on needle biopsy: prognostic and therapeutic implications and the utility of diagnostic markers. Pathology 2003; 35: 472–9.

480. Murphy WM, Dean PJ, Brasfield JA et al. Incidental carcinoma of the prostate. How much sampling is adequate? Am J Surg Pathol 1986; 10: 170–4.

481. Rohr LR. Incidental adenocarcinoma in transurethral resections of the prostate. Partial versus complete microscopic examination. Am J Surg Pathol 1987; 11: 53–8.

482. McDowell PR, Fox WM, Epstein JI. Is submission of remaining tissue necessary when incidental carcinoma of the prostate is found on transurethral resection? Hum Pathol 1994; 25: 493–7.

483. Littruop PJ, William CR, Egglin TK et al. Determination of prostate volume with transrectal US for cancer screening. II. Accuracy of in vitro and in vivo techniques. Radiology 1991; 179: 49–53.

484. Stamey TA, McNeal JE, Freiha FS et al. Morphometric and clinical studies on 68 consecutive radical prostatectomies. J Urol 1988; 139: 1235–41.

485. Montironi R, Mazzucchelli R, Barbisan F et al. Search for residual prostate cancer on pathological stage pT0 radical prostatectomies after positive core biopsy. Virch Arch 2007; 450: 371–8.

Section 5

Tumors of the seminal vesicles

Rodolfo Montironi, Roberta Mazzucchelli, Liang Cheng, and Antonio Lopez-Beltran

Tumors that arise in the seminal vesicles (SVs) as a primary site are rare (Table 5.1). Clinical presentations include pelvic pain and urinary or rectal obstructive symptoms. Some may be asymptomatic, and detected by digital rectal examination and sonography. Needle or open biopsy is required to establish the diagnosis. It may be difficult to ascertain the site of origin when adjacent pelvic organs are involved.

Epithelial tumors

Cystadenoma

Cystadenoma is a rare benign tumor. Patients range in age from 37 to 66 years. They may be asymptomatic or have symptoms of bladder outlet obstruction.[1,2] Ultrasound reveals a complex, solid-cystic pelvic mass.[3] Tumors may recur when incompletely removed.

Microscopically, cystadenoma is a well-circumscribed tumor containing variable-sized glandular spaces with branching contours and cysts separated by spindle cell stroma. The glands are grouped in a lobular pattern, contain pale intraluminal secretions, and are lined by one or two layers of cuboidal to columnar cells. No significant cytologic atypia, mitotic activity, or necrosis are present.[1,2,4]

Adenocarcinoma

The seminal vesicle is involved by secondary tumors much more frequently than it contains primary adenocarcinoma. *Strict criteria for the diagnosis of this lesion require the exclusion of a concomitant prostatic, bladder, or rectal carcinoma.*[5] Acceptable reported cases number 48.[5] Although most are in older men, 10 men were under age 40.[6,7]

Presenting symptoms usually include obstructive uropathy due to a non-tender peri-rectal mass[6,8] and, less commonly, hematuria or hematospermia. Serum carcinoembryonic antigen may be elevated.

The tumors are usually large (3–5 cm) and often invade the bladder, ureter, or rectum.[6,8] Tumors can show a mixture of glandular, papillary, and trabecular features with varying degrees of differentiation. Tumors with a colloid pattern have been described. Tumor cytoplasm may show clear cell or hobnail morphology.

It is important to exclude a prostatic adenocarcinoma using PSA and PAP immunohistochemistry.[9] Carcinoembryonic antigen (CEA) is detectable in normal seminal vesicle and seminal vesicle adenocarcinoma. Tumor should be positive for cytokeratin 7 (unlike many prostatic adenocarcinomas) and for CA125 (unlike carcinoma arising in a mullerian duct cyst) and negative for cytokeratin 20 (unlike bladder and colonic carcinoma).

The prognosis of primary seminal vesicle adenocarcinoma is poor.[6] Most patients present with metastases. Survival is less than 3 years in 95% of cases.

Benign and malignant mixed epithelial–stromal tumors

The criteria for the diagnosis of mixed epithelial–stromal tumors are reported in Table 5.2.[10–13]

Table 5.1 Tumors of the seminal vesicles

1. Epithelial tumors
   - Cystadenoma
   - Primary adenocarcinoma
2. Benign and malignant mixed epithelial stromal tumors
   - Fibroadenoma and adenomyoma
   - Malignant epithelial–stromal tumors (categorized as low-grade or high-grade)
3. Mesenchymal tumors (see Tables 3)
   - Benign
   - Malignant

Table 5.2 Criteria for the diagnosis of mixed epithelial stromal tumors originating in the seminal vesicles

1. They arise from the seminal vesicle
2. There is no normal seminal vesicle within the tumor
3. They usually do not invade the prostate (one exception was reported)[11]
4. They have a less conspicuous, less cellular stromal component than cystadenoma
5. They are not immunoreactive for prostatic markers or CEA

Fibroadenoma and adenomyoma

These tumors have occurred in men aged 39–66 who presented with pain and voiding difficulty. The lesions were grossly solid and cystic, ranging from 3 to 15 cm. The distinction from epithelial–stromal tumor of low-grade (below) is based on stromal blandness and inconspicuous mitotic activity.

Malignant epithelial–stromal tumors

Four cases have been reported.[10–13] The tumors occurred in men aged 49–61 who had urinary obstruction. One man was cured by cystoprostatectomy;[11] two had pelvic recurrence after 2 years, one cured by a second excision[13] and one surgically incurable;[12] and one developed lung metastasis 4 years after the operation.[10]

Macroscopically, the tumors are either multicystic or solid and cystic. Microscopically, the stroma is at least focally densely cellular and tends to condense around distorted glands lined by cuboidal to focally stratified epithelium. The tumors are categorized as low-grade or high-grade, depending on mitotic activity and necrosis.

Mesenchymal tumors

Table 5.3 reports the list of mesenchymal tumors observed in the SVs.

Angiosarcoma

Three cases were reported[14–16] and all presented with pelvic pain. Two died of distant metastasis within 2 months after the diagnosis.[14,15]

Table 5.3 Mesenchymal tumors of the seminal vesicles

- Angiosarcoma
- Hemangiopericytoma
- Leiomyosarcoma
- Leiomyoma
- Liposarcoma
- Malignant fibrous histiocytoma
- Solitary fibrous tumor
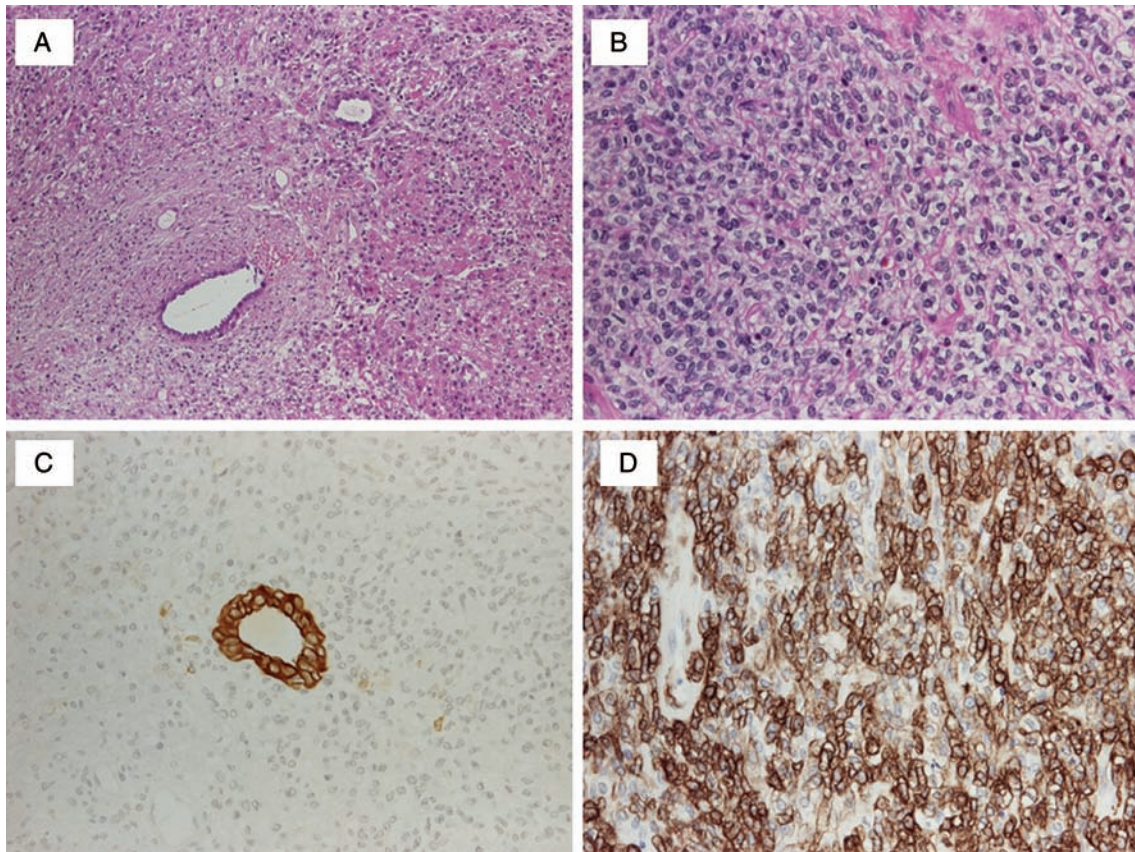
Figure 5.1

(A) Leiomyosarcoma involving the wall of the seminal vesicle. (B) Leiomyosarcoma with epithelioid features. (C) Residual seminal vesicle epithelium highlighted by immunohistochemistry (antibody against cytokeratin AE1–AE3). (D) Desmin expression in the leiomyosarcoma.

Hemangiopericytoma

A case of malignant hemangiopericytoma of the seminal vesicle has been reported by Arya and colleagues.[17] The patient was treated by cystoprostatectomy and vesiculectomy and died of disseminated hemangiopericytoma 10 years later.

Leiomyoma

It is usually asymptomatic. Among the seven reported cases, six were detected on digital rectal examination and one by magnetic resonance imaging.[18,19] The tumor measures up to 5 cm.[19] Local excision has yielded no recurrences.

Leiomyosarcoma

By digital rectal examination and pelvic computed tomography as well as magnetic resonance imaging, a large pelvic mass in the region of the SVs of the prostate is seen. Six patients with reported seminal vesicle leiomyosarcoma presented with pelvic pain and obstructive symptoms.[20–22] Resection of the tumor mass by radical prostatectomy and vesiculectomy is the therapy of choice. One patient was cured by radical cystoprostatectomy at 13-month follow-up,[20] although another developed renal metastasis after 2 years.[21] Morphologically it is identical to leiomyosarcoma of other locations (Figure 5.1).

Liposarcoma

There is one case described as a 'collision' tumor composed of liposarcoma of the SVs and prostatic carcinoma.[23] The patient died of distant metastasis from prostatic carcinoma.

Malignant fibrous histiocytoma

This tumor is exceedingly rare in the seminal vesicle.[24] Sonographic investigations are important to establish the site of origin. The therapy should be the complete surgical resection, in most cases by radical prostatectomy and vesiculectomy.

Solitary fibrous tumor

Three cases have been reported,[25,26] and all were located in the right seminal vesicle. The origin of the tumor was established by transrectal ultrasonography, magnetic resonance imaging, or computed tomography. The clinical presentations were pelvic pain or hematuria. Complete local excision appears to be curative.

References

1. Baschinsky DY, Niemann TH, Maximo CB, Bahnson RR. Seminal vesicle cystadenoma: a case report and literature review. Urology 1998; 51: 840–5.
2. Santos LD, Wong CS, Killingsworth M. Cystadenoma of the seminal vesicle: report of a case with ultrastructural findings. Pathology 2001; 33: 399–402.
3. Lagalla R, Zappasodi F, Lo CA, Zenico T. Cystadenoma of the seminal vesicle: US and CT findings. Abdom Imaging 1993; 18: 298–300.
4. Mazzucchelli L, Studer UE, Zimmermann A. Cystadenoma of the seminal vesicle: case report and literature review. J Urol 1992; 147: 1621–4.
5. Ormsby AH, Haskell R, Ruthven SE, Mylne GE. Bilateral primary seminal vesicle carcinoma. Pathology 1996; 28: 196–200.
6. Benson RC Jr, Clark WR, Farrow GM. Carcinoma of the seminal vesicle. J Urol 1984; 132: 483–5.
7. Kindblom LG, Pettersson G. Primary carcinoma of the seminal vesicle. Case report. Acta Pathol Microbiol Scand [A] 1976; 84: 301–5.
8. Oguchi K, Takeuchi T, Kuriyama M, Tanaka T. Primary carcinoma of the seminal vesicle (cross-imaging diagnosis). Br J Urol 1988; 62: 383–4.
9. Ormsby AH, Haskell R, Jones D, Goldblum JR. Primary seminal vesicle carcinoma: an immunohistochemical analysis of four cases. Mod Pathol 2000; 13: 46–51.
10. Fain JS, Cosnow I, King BF et al. Cystosarcoma phyllodes of the seminal vesicle. Cancer 1993; 71: 2055–61.
11. Laurila P, Leivo I, Makisalo H et al. Mullerian adenosarcomalike tumor of the seminal vesicle. A case report with immunohistochemical and ultrastructural observations. Arch Pathol Lab Med 1992; 116: 1072–6.
12. Maheshkumar P, Harper C, Sunderland GT, Conn IG. Cystic epithelial stromal tumour of the seminal vesicle. BJU Int 2000; 85: 1154.
13. Mazur MT, Myers JL, Maddox WA. Cystic epithelial-stromal tumor of the seminal vesicle. Am J Surg Pathol 1987; 11: 210–17.
14. Chiou RK, Limas C, Lange PH. Hemangiosarcoma of the seminal vesicle: case report and literature review. J Urol 1985; 134: 371–3.
15. Lamont JS, Hesketh PJ, de las MA, Babayan RK. Primary angiosarcoma of the seminal vesicle. J Urol 1991; 146: 165–7.
16. Panageas E, Kuligowska E, Dunlop R, Babayan R. Angiosarcoma of the seminal vesicle: early detection using transrectal ultrasound-guided biopsy. J Clin Ultrasound 1990; 18: 666–70.
17. Arya M, Hayne D, Brown RS et al. Hemangiopericytoma of the seminal vesicle presenting with hypoglycemia. J Urol 2001; 166: 992.
18. Bahn DK, Brown RK, Shei KY, White DB. Sonographic findings of leiomyoma in the seminal vesicle. J Clin Ultrasound 1990; 18: 517–19.
19. Gentile AT, Moseley HS, Quinn SF et al. Leiomyoma of the seminal vesicle. J Urol 1994; 151: 1027–9.
20. Amirkhan RH, Molberg KH, Wiley EL et al. Primary leiomyosarcoma of the seminal vesicle. Urology 1994; 44: 132–5.
21. Muentener M, Hailemariam S, Dubs M et al. Primary leiomyosarcoma of the seminal vesicle. J Urol 2000; 164: 2027.
22. Schned AR, Ledbetter JS, Selikowitz SM. Primary leiomyosarcoma of the seminal vesicle. Cancer 1986; 57: 2202–6.
23. Juhasz J, Kiss P. A hitherto undescribed case of 'collision' tumour: liposarcoma of the seminal vesicle and prostatic carcinoma. Int Urol Nephrol 1978; 10: 185–93.
24. Dahms SE, Hohenfellner M, Linn JF et al. Retrovesical mass in men: pitfalls of differential diagnosis. J Urol 1999; 161: 1244–8.
25. Morin G, Houlgatte A, Camparo P et al. (Solitary fibrous tumor of the seminal vesicles: apropos of a case.) Prog Urol 1998; 8: 92–4.
26. Westra WH, Grenko RT, Epstein J. Solitary fibrous tumor of the lower urogenital tract: a report of five cases involving the seminal vesicles, urinary bladder, and prostate. Hum Pathol 2000; 31: 63–8.

Section 6

Tumors of the testis and paratesticular structures

Gregor Mikuz and Maurizio Colecchia

Introduction

The clinical term 'testicular tumor' is a synonym for all intrascrotal masses regardless of their actual anatomic location. In fact, some 90% of tumors in the scrotum arise in the testis,[1] and at least 90% of them belong to the group of germ cell tumors (GCTs). Intrascrotal tumors are classified according to the WHO (2004) classification,[2] based on their histologic features and anatomic location. The classification includes 8 major groups (Table 6.1): *germ cell tumors, sex cord/gonadal*

Table 6.1 WHO 2004 classification[2] of testicular tumors

Germ cell tumors	ICD-O
Intratubular germ cell neoplasia, unclassified	9064/2
Other types	
Tumors of one histologic type (pure forms)	
Seminoma	9061/3
Seminoma with syncytiotrophoblastic cells	
Spermatocytic seminoma	9063/3
Spermatocytic seminoma with sarcoma	
Embryonal carcinoma	9070/3
Yolk sac tumor	9071/3
Trophoblastic tumors	
Choriocarcinoma	9100/3
Trophoblastic neoplasms other than choriocarcinoma	
Monophasic choriocarcinoma	
Placental site trophoblastic tumor	9104/3
Teratoma	9080/3
Dermoid cyst	9084/0
Monodermal teratoma	
Teratoma with somatic type malignancies	9084/3
Tumors of more than one histologic type (mixed forms)	
Mixed embryonal carcinoma and teratoma	9081/3
Mixed teratoma and seminoma	9085/3
Choriocarcinoma and teratoma/embryonal carcinoma	9101/3
Others	
Sex cord/gonadal stromal tumors	
Pure forms	
Leydig cell tumor	8650/1
Malignant Leydig cell tumor	8650/3
Sertoli cell tumor	8640/1
Sertoli cell tumor lipid rich variant	8641/1
Sclerosing Sertoli cell tumor	
Large cell calcifying Sertoli cell tumor	8642/1
Malignant Sertoli cell tumor	8640/3
Granulosa cell tumor	8620/1
Adult type granulosa cell tumor	8620/1
Juvenile type granulosa cell tumor	8621/1
Tumors of the thecoma/fibroma group	
Thecoma	8600/0
Fibroma	8810/0
Sex cord/gonadal stromal tumor incompletely differentiated	8591/1
Sex cord/gonadal stromal tumor, mixed forms	8592/1
Malignant sex cord/gonadal stromal tumor	8590/3
Tumors containing both germ cell and sex cord/gonadal stromal element	
Gonadoblastoma	9073/1
Germ cell–sex cord/gonadal stromal tumor, unclassified	

(*Continued*)

Table 6.1 (Continued)

Miscellaneous tumors of the testis	
Carcinoid tumor	8240/3
Tumors of ovarian epithelial types	
Serous tumor of borderline malignancy	8442/1
Serous carcinoma	8441/3
Well-differentiated endometrioid carcinoma	8380/3
Mucinous cystadenoma	8470/0
Mucinous cystadenocarcinoma	8470/3
Brenner tumor	8960/3
Nephroblastoma	8680/1
Paraganglioma	
Hematopoietic tumors	
Tumors of collecting ducts and rete	
Adenoma	8140/1
Carcinoma	8140/3
Tumors of paratesticular structures	
Adenomatoid tumor	9054/0
Malignant mesothelioma	9050/3
Benign mesothelioma	
Well-differentiated papillary mesothelioma	9052/0
Cystic mesothelioma	9055/0
Adenocarcinoma of the epididymis	8140/3
Papillary cystadenoma of the epididymis	8450/0
Melanotic neuroectodermal tumor	9363/0
Desmoplastic small round cell tumor	8806/3
Mesenchymal tumors of the spermatic cord and testicular adnexae	
Secondary tumors of the testis (metastases)	

Table 6.2 The original British Testicular Tumor Panel classification[1]

1. Tumors of the testis	
Seminoma:	Classical
	Spermatocytic
Teratoma:	Teratoma differentiated (TD)
	Malignant teratoma intermediate (MTI) with differentiated or organoid components, but also containing undifferentiated elements
	Malignant teratoma undifferentiated (MTU) with no mature tissue or organoid structures
	Malignant teratoma trophoblastic (MTT)
Combined tumor:	Seminoma and teratoma in the same testis (CT)
Sertoli cell/mesenchyme tumors (SMT)	
Interstitial cell tumors (ICT)	
Yolk-sac tumors	
Malignant lymphomas	
Miscellaneous tumors	

(*Continued*)

Table 6.2 (Continued)

Metastases
Tumors of uncertain diagnosis

2. Tumors of epididymis and cords
Adenomatoid tumor
Tumors of connective tissue and muscle
  subdivided into:
  Benign: Fibroma, leiomyoma, lipoma, etc.
  Malignant: Embryonic sarcoma,[a] fibrosarcoma,
                      leiomyosarcoma, etc.
Miscellaneous tumors
Metastases
Tumors of uncertain diagnosis

[a] Old fashioned name for embryonal rhabdomysarcoma.

stromal tumors, miscellaneous tumors of the testis, hematopoietic tumors, tumors of collecting ducts and rete, tumors of paratesticular structures, mesenchymal tumors, and secondary tumors (metastases). The so-called 'British Classification' (Table 6.2) proposed by the British Testicular Tumor Panel in the early 1960s[1,3] was widely used in Europe until the end of the 1990s. It is slowly disappearing because the new WHO classification has consensually been accepted by pathologists specializing in this field. Furthermore, new cytogenetic and molecular pathologic data strongly support the theoretic background of this classification.

Although rare, germ cell tumors have always been of great interest to pathologists, due to their peculiar biology and morphology, and for the clinician as well, because they are deadly tumors which nowadays can be cured in more than 90% of cases.

With the exception of malignant lymphomas, which are the second most frequent tumors of the testis, all other morphologic entities are only rarely encountered, even by urologists working in large urologic departments.

Part 1

Germer cell tumors

Principles of classification

It took more than half a century to construct a histologic classification of germ cell tumors (GCTs) properly reflecting the enormous morphologic variety of these tumors as well as their probable histogenesis. The discovery of a precursor lesion,[4] originally called '*carcinoma in situ of the testis*' (CIS), supported the theoretic background of the WHO classification originally proposed by Mostofi and Sobin in 1977.[5] All recent investigations show definitively that all different types of GCTs derive from a neoplastic precursor cell, which is capable of differentiation along differing pathways. In accordance with morphologic reality, the WHO 2004 classification[2] distinguishes between GCTs of one histologic type (pure forms) and those with a mixture of two or more different histologic patterns (mixed forms) (Table 6.1). Almost half (40–50%) of all GCTs are pure seminomas; a third are mixed forms of non-seminomatous tumors (NSGCTs) including combinations with seminomas; and only 14–16% are pure NSGCTs.[6–9]

In pragmatic fashion, the British Classification (BC) reduced the great variety of the GCTs' histology to a few categories, easily understandable to non-specialized pathologists and clinicians.[1,3] According to the BC only seminomas are of germ cell origin, all other 'non-seminomatous' tumors, called teratoma, derive from displaced embryonic blastomers – a theory which has not been proven. According to the degree of differentiation, teratomas are subdivided into a *differentiated* (DT), an *undifferentiated* (MTU), an *intermediate* (MTI), and a *trophoblastic type* (MTT). Yolk sac tumor is an entity assumed to arise only in infant's testis; thus, in adults the pure form (extremely rare) is classified as MTU and the combination with differentiated teratoma as MTI. The mixture of seminoma and any type of teratoma is called *combined tumor*. Since the BC has never been updated, some important entities are missing. Furthermore, this simple, manageable classification does not conform with modern findings on the pathohistogenesis of these tumors.

A diagnosis of the WHO classification can easily be transformed into that of the BC, whereas vice versa is utterly impossible (Table 6.3).

Histogenesis of GCTs

It has been proposed that CIS cells develop from primordial germ cells and early gonocytes,[10,11] because all these cells express immunohistochemical markers not found in adult germ epithelium, but also found in overt GCTs. Placenta-like alkaline phosphatase (PlAP) was the first marker described[12] in CIS and seminoma. Of even greater importance for an understanding of the oncogenesis is the discovery of factors essential for maintaining pluripotency and self-renewal capability of embryonal stem cells (c-KIT, AP- 2γ , OCT-3/4),[11] which shows that CIS cells closely resemble embryonic stem cells. Furthermore, factors such as AP-2γ, confined to undifferentiated somatic tissue, may explain why GCTs are capable of differentiating into various somatic tissue components.

CIS cells are supposed to differentiate from primordial germ cells and/or gonocytes which failed to mature into normal germ cells, in

Table 6.3 Comparison of the WHO 2004 and British Classification of the germ cell tumors of the testis

British	WHO
Seminoma	Seminoma
Spermatocytic seminoma	Spermatocytic seminoma
Teratoma differentiated	Teratoma
Malignant teratoma intermediate	Teratoma+any combination with embryonal carcinoma and/or yolk sac tumor
	Teratoma with somatic type malignancies
Malignant teratoma undifferentiated	Embryonal carcinoma with or without yolk sac tumor
Malignant teratoma trophoblastic	Any combination of choriocarcinoma with NSGCTs
Yolk sac tumor	Only pure form of YST
Combined tumor	Seminoma+any combination of NSGCTs

NSGCT = non-seminomatous tumor.

which the transcriptional factors are normally regulated downwards. A disturbance of the microenvironment due to exogenous hormonal misbalance and/or genetic factors (intersex) could initiate the neoplastic transformation. Genomic changes would give the CIS cells an anti-apoptotic and proliferative advantage.

The best support for the theory of the common origin of the GCTs is the isochromosome i(12p) – a chromosome with four short arms present in about 80% of GCTs regardless of their morphology. NSGCTs usually have more copies of chromosome i(12p) than seminomas.[13] Amplification of 12p leads to deregulated overexpression of cyclin D2, a cell cycle G1/S checkpoint regulator with oncogenic potential. As a consequence of the deregulation, CIS becomes invasive. Although p53 protein is highly expressed in the majority of GCTs, almost no p53 mutations have been detected. Gain of mdm2 expression might induce a partial loss in functionality of the p53 regulatory pathway in GCTs and promote the invasiveness of CIS.[14,15]

Since pediatric GCTs (mostly yolk sac tumors and teratomas) and spermatocytic seminomas of elderly men do not show CIS in the surrounding testicular tissue, the cancerization probably follows a different path. Due to genomic aberrations pediatric GCTs could directly develop from the primordial germ cells.[11] Spermatocytic seminoma seems to develop from more differentiated germ cells such as spermatogonia or spermatocytes. Some authors speculate that the tumor arises through self-fertilization of the germ cells.[12]

The direct descendant of CIS is probably the seminoma, because its cells strongly resemble CIS cells and also manifest the same immunohistochemical markers. Embryonal carcinomas (ECs) develop from seminomas, although there is some evidence they can also derive directly from CIS. ECs can undergo a somatic

transformation to teratoma or an extra embryonic one to yolk sac tumor and choriocarcinoma. The proposed sequence is based on histologic observations and seems to be the most reliable and the most frequent. Deviations from this sequence are purportedly possible but infrequent (Figure 6.1).

Epidemiology

GCTs account for only 1–2% of malignant tumors in males and more than 90% of intrascrotal tumors. There is no doubt that race is one of the most important etiologic factors in the development of GCTs. White men living in Western industrialized countries show the highest incidence rates[16] (Table 6.4), whereas black men in Africa show the lowest.[16] The incidences in Asiatic men lie somewhere between both extremes. Maoris from New Zealand (incidence = $7.1/10^5$) are an exception to this racial factor. The average incidence rate in Europe and USA accounts for $5–6/10^5$ – the highest rates of $\geq 10/10^5$ are observed in Denmark, Norway, and Switzerland.[16,17] The remarkable average difference between more ($4.5/10^5$) and less ($0.8/10^5$) developed countries is a strong argument in favor of the influence of environmental carcinogens. In the last decade, incidence rates increased worldwide by up to 70%, even among African Americans[18] and in countries with low rates.[16,17] The incidence of GCTs is somewhat lower ($2/10^5$) in children and accounts for 1% of all pediatric neoplasms.[19] Similarly to adults, GCTs are more frequent in white than in black children. More than one-third of testicular tumors in children do not originate from germ cells but from specialized gonadal stroma, or they are typical pediatric lymphomas.

Very few causes other than race, listed and discussed below, are statistically correlated with the growth of GCTs. Some tumors are either genetically triggered or related to other diseases or development anomalies of the genital organs. Many exogenous substances
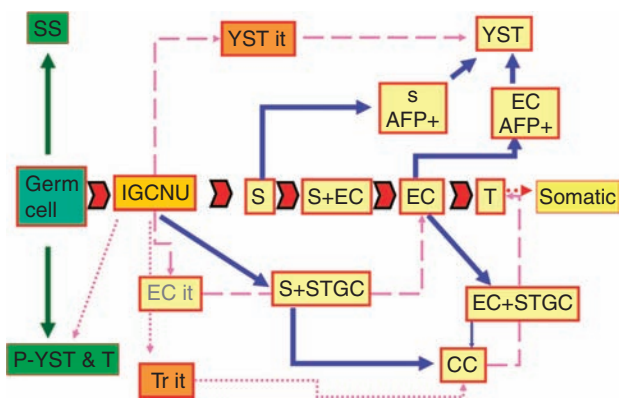
Figure 6.1

The hypothetical development of the testicular germ cell tumors according to Ulbright et al.[138] The direct descendant of IGCNU is probably the seminoma (S). Embryonal carcinomas (EC) develop from seminomas. EC can undergo a somatic transformation to teratoma (T) or an extra embryonic one to yolk sac (YST) tumor and choriocarcinoma (CC). Somatic type tumors develop from teratoma. Deviations from this sequence are purportedly possible but infrequent. it = intratubular; SS = spermatocytic seminoma; STGC = syncytiotrophoblastic cells; P = pediatric.

Table 6.4 Annual age-adjusted[a] (world population) incidence and mortality of testicular tumors in some selected countries geographical per 100 000 male population/year[16]

Country	Incidence	Mortality
Eastern Europe average	**2.6**	**0.6**
Belarus	1.8	0.7
Bulgaria	3.2	0.8
Czech Republic	6.8	0.7
Hungary	5.6	0.9
Moldova	4.0	0.6
Poland	4.1	0.5
Romania	3.2	0.6
Russian Federation	1.9	0.6
Slovakia	3.6	0.5
Ukraine	1.8	0.8
Northern Europe average	**6.2**	**0.3**
Denmark	10.3	0.4
Estonia	2.2	0.6
Finland	3.2	0.2
Iceland	5.9	0.0
Ireland	5.3	0.4
Latvia	2.1	0.6
Lithuania	1.4	0.6
Norway	11.0	0.3
Sweden	5.8	0.2
United Kingdom	6.5	0.3
Western Europe average	**7.9**	**0.4**
Austria	8.8	0.4
Belgium	5.0	0.2
France	6.7	0.3
Germany	9.2	0.4
Luxembourg	7.6	0.0
The Netherlands	5.8	0.3
Switzerland	10.1	0.4
Southern Europe average	**3.0**	**0.3**
Albania	3.8	0.5
Bosnia	4.7	0.5
Croatia	5.5	0.6
Greece	3.0	0.2
Italy	2.9	0.2
Macedonia	4.0	0.8
Malta	3.1	0.7
Portugal	4.6	0.3
Serbia & Montenegro	3.8	0.4
Slovenia	8.6	0.4
Spain	1.9	0.1
Australia/New Zealand	5.7	0.3
USA white	5.6	0.2
USA black	1.04	0.2
Canada	4.6	0.2
Central America	2.9	0.7
South America	2.4	0.5
Africa	0.4–0.9	0.2–0.4
Caribbean	0.8	0.3
Eastern Asia	0.5–1.4	0.1–0.5
Japan	1.6	0.2
China	0.4	0.1

[a]Crude incidence rates are on average around 0.1–0.5 higher than the age-adjusted ones.

have been blamed for causing testicular cancer, but clear epidemiologic evidence is lacking for most of them.

Some well-established epidemiologic causes are listed below. However, not all relative risk figures have the same level of evidence (Table 6.5), which depends mainly on the reliability of the studies.[20] The level of evidence is higher in cohort studies than in case series or case reports and when the results of different studies are homogeneous.

Cryptorchidism has been strongly related to risk of GCTs in many different studies. The relative risk (RR) reported ranges from 2.1 to 17.6.[21,22] The RR in men who were treated for cryptorchidism increased with age at treatment. Successful treatment after one's 11th birthday or never corresponds to *a 32-fold increased risk*.[21] Men with a history of undescended testes which descended spontaneously seem not to be at risk.[21] Whether orchipexy reduces the incidence of tumors is, however, still controversial.[21–24] There are many different ideas about the mechanism which predisposes cryptorchid testes for GCTs. Most popular at the moment is the *testicular dysgenesis syndrome* hypothesis, which proposes that the four conditions cryptorchidism, hypospadias, impaired spermatogenesis, and testis cancer may all be manifestations of disturbed prenatal testicular development,[25] which is caused by environmental factors. There is weak epidemiologic evidence that substances acting like estrogen called *estrogen disruptors or xenestrogens* (polychlorinated biphenyls, polybrominated biphenyls, persistent pesticides (DDT) and phthalate esters) induce an early menarche in girls and delay puberty in boys.[26,27] Findings in animals experimentally exposed to exogenous estrogens as well as observations in wildlife (feminization of panthers, intersex fishes) support this theory. The action of endocrine disruptors could be enhanced by a genetic predisposition for GCTs.

Contralateral GCTs: the incidence of metachronous contralateral GCTs reported in most series accounts for 3% and is higher for patients with seminoma than for non-seminomatous tumors.[20,28] The estimated risk in different studies seems to be even higher (25-fold) than for cryptorchidism;[20] the results of different studies are, however, not as well documented as those for retained testes.

Familial GCTs: testicular cancer shows a strong familial association, which is probably partly genetic, partly environmental.[29] The risk is 3.8-fold when a father and 7.6-fold when a brother had testicular cancer.[30] The higher familial risk for testicular cancer among brothers than father–son pairs may suggest the involvement of a

recessive mode of inheritance or an X-linked susceptibility locus in the etiology of testicular cancer. Patients with familial testicular cancer had 3 times more frequent (9.8% vs 2.8%) bilateral tumors than sporadic cases.[30,31] A testicular GCT susceptibility gene at Xq27, probably also responsible for familial cases of cryptorchidism, has been reported. New investigations suggest, however, that multiple susceptibility loci with weak effects can contribute to the disease.[32]

Gonadal dysgenesis: the formation of GCTs (mostly gonadoblastomas) in dysgenetic gonads occurs, according to literature data, in 20–30% of cases and is associated with the presence of the Y chromosome in the patient's karyotype.[33,34] It is usually diagnosed at a young age.[33]

Male infertility: the RR of infertile men to suffer a GCT is rather high (relative risk 1.6–10) and probably due to the same factors which are blamed for causing cryprorchidism (*testicular dysgenesis syndrome*). Moreover, the most frequent genetic cause of idiopathic infertility, the deletion of the AFZc at Yq11 (azoospermia factor c), is also somehow related to the oncogenesis of GCTs.[35]

Testicular atrophy has been identified as cancer-related in some studies;[20,22] the risk ranges from 2.7 to 12.7.[20]

Surgery (trauma), namely, vasectomy, orchipexy, and inguinal herniorophy, represent a RR of 1.1–2.9.[20] The data on testicular torsion are not conclusive.[20,22]

Infectious diseases: many infectious diseases (mumps, tuberculosis, HIV) have been connected with GCTs, although the results of controlled studies are heterogeneous and not really conclusive.[20] A possible role of Epstein–Barr virus (EBV) in the pathogenesis of TGCTs has been suggested repeatedly, but direct evidence for an association of testicular cancer with EBV is lacking. A recent study found EBV only in the lymphocytes scattered in seminomas, but not in the neoplastic cells, which makes a direct role of EBV in the development of these malignancies improbable.[36]

Occupational exposure to noxious conditions has been explored in many studies, yet no specific conditions or substance have been unanimously confirmed.[20] The professions at risk reported in the literature are: firefighters, aircraft technicians, maintenance workers at paper mills, leather workers, and metal workers. A Finnish study proposes only four occupations at high risk (RR CI 1.1–14.7): railway traffic supervisors, systems analysts (programmers), university teachers, and electrical engineers.[37] The often reported high incidence of those employed in agriculture[20,38] is obviously a response to exposure to pesticides and organic dusts.[39]

The estrogen theory: as already mentioned (cryptorchidism) Scandinavian scientists[25,26] have hypothesized that estrogen disruptors lead indirectly to testis cancer. The conditions – first born (RR 1.0–41), mother older than 30 (RR 0–2.3), mother with breast cancer (RR 0–2.1), and a birth weight under 2.5 kg (RR 1.0–13.5) – have been used as surrogate parameters for gestational estrogen excess.[20] The findings of the different studies show an extreme variability, making the use of such surrogates questionable.

Socio-economic status: an association with high socio-economic status was observed as early as 1921 and confirmed in many subsequent studies.[20,40] High calorie intake during early childhood, obviously more common in wealthy than poor people, was a tentative explanation for the association, which has never been proven. With the merging of social classes in modern society, the association between high GCT incidence and white collar workers also becomes less clear.[40]

Testicular microlithiasis: (Figures 6.2 and 6.3) is obviously not a cause of testis cancer, but is clinically important because it is frequently associated with testicular germ cell tumors (TGCTs) (Table 6.6). The detection of the lesion often occurs accidentally with imaging techniques (CAT scan, ultrasonography) in connection with

---

Table 6.5 Putative causes of TGCTs and the estimated relative risk

Cryptorchidism	2–17-fold
Contralateral TGCT	25-fold
Familial TGCT	3.8–7.6-fold
Gonadal dysgenesis	30–50-fold
Male infertility	1.6–10-fold
Testicular atrophy	2.7–12.7-fold
Surgery (trauma)	1.1–2.9-fold
Infectious diseases	? probably no risk
Occupational exposure	1.1–14.7-fold
Mother older than 30	0–2.3-fold
Mother breast cancer	0–2.1-fold
Birth weight < 2.5 kg	1–13.5-fold
High socioeconomic status	? probably no risk
Microlithiasis*	*6–46% GCT prevalence!*

* Not a risk factor but an associated lesion.
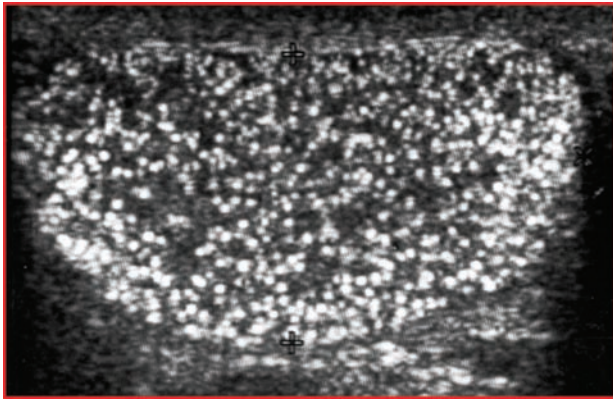
Figure 6.2
Ultrasound appearance of testicular microlithiasis.
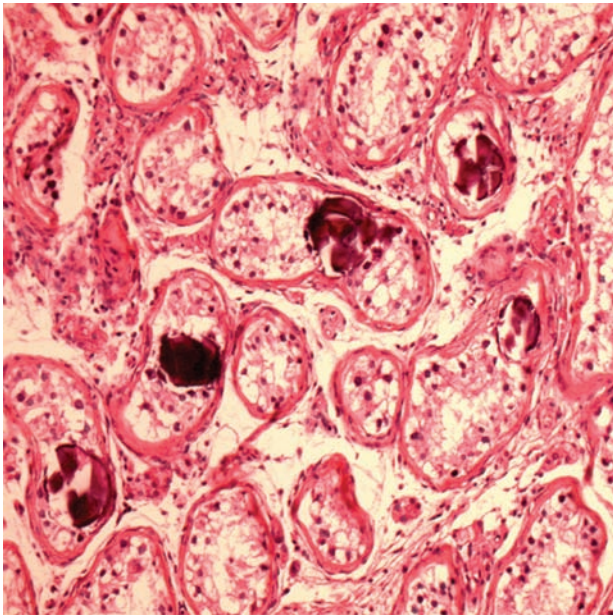
Figure 6.3
Intratubular calcifications (microlithiasis) in testicular parenchyma adjacent to a germ cell tumor.

Table 6.6 Conditions associated with testicular microlithiasis
■ TGCT
■ IGCNU
■ Cryptorchidism
■ Infertility
■ Down syndrome
■ Inflammation

Table 6.7 The typical age of patients with the various TGCTs	
Seminoma	Average age 35–40
	Extremely rare before puberty
	Rare after 70
Spermatocytic seminoma	> 40 years
Embryonal carcinoma	Average age 30
	Rare before puberty
Teratoma (pure form)	Average age in children = 20 months
	Rare after the age of 4
	Adults 20–30
Yolk sac tumor (pure form)	Average age 25–30 years
	15–40% of TGCTs in children
Choriocarcinoma	Average age 25–30 years
Mixed forms	28 years if non-seminomatous component prevails 33 years if seminoma prevails

diagnostic procedures performed for other reasons. The reported prevalence in the general population ranges from 0.6 to 9% and the incidence of GCTs in patients with microlithiasis was reported as 6–46%.[41] The unknown true incidence of microlithiasis-associated tumors is more likely to be at the lower than the upper end of the wide scale of the reported values (3–6%).

Age at orchiectomy

The average age (Table 6.7) of patients is significantly correlated with the morphology of the GCTs (see details for single tumors). Seminoma patients (30–34 years) are on average older than patients with NSGCTs (20–29 years). Even patients with mixed GCTs in which the seminoma dominates are older than those without or with a small amount of seminoma. GCTs, with the exception of spermatocytic seminomas, are extremely rare in men older than 60. As of that age malignant lymphomas with primary manifestation in the testis are the most frequent tumors in this location. In children before puberty, yolk sac tumors and teratomas are the most common GCTs.

Part 2

Intratubular germ cell neoplasia, unclassified (IGCNU)

Intratubular germ cell neoplasia is the official name of the lesion, better known as *carcinoma in situ* of the testis, the name used by Skakkebaek[4] in the first description of this lesion in 1972. Other names mostly used in German-speaking countries were *testicular intratubular neoplasia* (TIN),[42] in analogy to other intra-epithelial neoplasia, or simply *atypical germ cells*.[43,44] The adjective *unclassified* is utilized to emphasize that the morphology of the tumor cells does not permit an assignment to a definite type of GCT. If the intratubular tumor cells can be definitely recognized, the adjective *intratubular* is used in connection with the respective name of the GCT (i.e. intratubular seminoma, intratubular embryonal carcinoma, etc.).

Epidemiology

The true prevalence (Table 6.8) of this lesion in healthy men is, roughly estimated, 0.4–0.8% and about 1% in infertile men.[45] In cryptorchid testes of adults the frequency is 2–4%. In retained testes of prepubertal children, atypical germ cells can hardly be distinguished from normal immature spermatogonia.[45] High incidences (up to 20%) are found in the testes of hermaphrodites and, as already mentioned, in the contralateral testis of patients with GCT (4–6%).[42,46] With the exception of spermatocytic seminoma, atypical germ cells are constantly found (98%) in the healthy tissue surrounding invasive GCTs of adults.[46] IGCNUs can be also found in testicular biopsies of nearly 50% of patients with retroperitoneal extragonadal GCTs,[47] but only rarely in those of such tumors located in mediastinum[48] – and obviously never in intracranial GCTs.

Morphology

Affected testes appear normal and do not show any gross visible alteration unless they are atrophic and firm for other reasons (cryptorchidism). The atypical germ cells are attached to the usually thickened basement membrane and push the Sertoli cells towards the lumen of the seminiferous tubules (Figure 6.4). The cytoplasm is clear because of the large amount of glycogen which stains purple with PAS. The nuclei are bigger than those of spermatogonia and
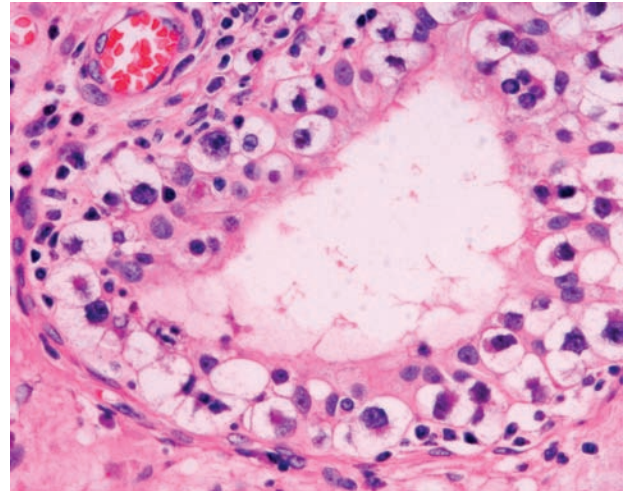
Figure 6.4

IGCNU: atypical germ cells with clear cytoplasm and slightly polymorphous nuclei.
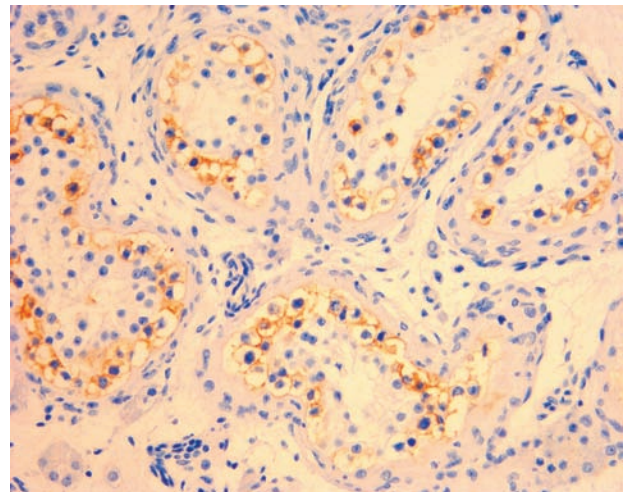
Figure 6.5

Atypical germ cells (brownish) positively stained with PlAP antibodies.

contain one or more nucleoli. Mitoses are frequent but may be overlooked. Lymphocytic infiltration of the interstitial tissue surrounding the affected, mostly clearly narrowed tubules is frequent. Atypical germ cells stain (Figure 6.5) immunohistochemically with PlAP, c-KIT (CD117), and OCT 3/4 antibodies and can thus easily be distinguished from non-reacting normal spermatogonia, which

Table 6.8 Prevalence of IGCNU	
Healthy men	0.4–0.8%
Infertile men	1.0%
Cryptorchid testis of adults	2–4%
Intersex	20%
Patients with TGCT – contralateral testis	4–6%
Retroperitoneal 'extragonadal' GCT	50%

are also glycogen (PAS)-negative. The 'maturation arrest' on the level of spermatogonia in biopsies of infertile men can be mistaken for IGCNU!

The atypical germ cells can grow and fill the lumen of the tubules and/or break through the lamina propria and invade the interstitial tissue. They can also spread in a 'pagetoid' pattern into the rete testis. The cells of microinvasive IGCN are still undifferentiated although mostly very similar to the spermatogonia.

Cytogenetics

IGCNU cells are aneuploid[49] and show the chromosomal aberrations found later on in invasive TGCT, with clear differences between seminoma and NSGCT.[50] They gain i(12p) copies only shortly before they become microinvasive.[51]

Clinical features

IGCNU is a purely histopathologic diagnosis and does not produce any symptoms. The lesion can be found accidentally in testicular biopsies performed for the assessment of infertility or in biopsies of the contralateral testis in men with unilateral TGCT.[52,53] There is no consensus about the necessity of routinely performing such biopsies. The majority of European urologists advocate this policy.[54,55] Opponents claim the patients were unnecessarily worried, since only 5.5% of patients with TGCTs have this lesion in the contralateral testis and bilateral testicular tumors are even less frequent (3%), which means that IGCNUs can spontaneously regress.[56] Furthermore, patients with TGCTs are continuously controled and therefore a second tumor would be detected in an early and curable stage. However, 50% of men with IGCNU will develop testicular cancer 5 and 90% 7 years after detection of the lesion.[52]

For the complete destruction of IGCNU the testis must be irradiated with 18–20 Gy.[54] Chemotherapy does not have any therapeutic effect.[57]

IGCNU is randomly spread in the seminiferous tubules or equally distributed in certain small segments of the organ. To avoid false negative results (0.5% of single biopsies) two biopsies per organ increase the probability of detection and are therefore recommended.[54]

Part 3

Seminomas

Seminoma

Epidemiology

Almost half of all intrascrotal tumors are seminomas (Table 6.9). Their incidence has dramatically increased in white men in the US (60%) over the last two decades.[58] Patients are on average 30–34 years old and are the oldest men of all with TGCT.[58] Nevertheless they have recently become significantly younger because in old series the average age was 41 years.[59,60] Seminoma does not occur before puberty and is rare (1%) in adolescents[61] as well as in men older than 60. Single cases, however, have also been observed in octogenarians.[59] Of these patients, 8% have a history of maldescent, etc.

Morphology

The affected testis is usually enlarged, but can be normal or even atrophic. The tumor is uniform, cream-colored or pink, and always well-circumscribed (Figure 6.6). The cut surface is lobulated and the consistency varies from soft to firm, depending on the amount of tumor stroma. Nowadays in the majority of cases the tumors are confined to the testis, but extension to the epididymis and spermatic cord can occur and were very frequent (43%) in old series.[60] In large
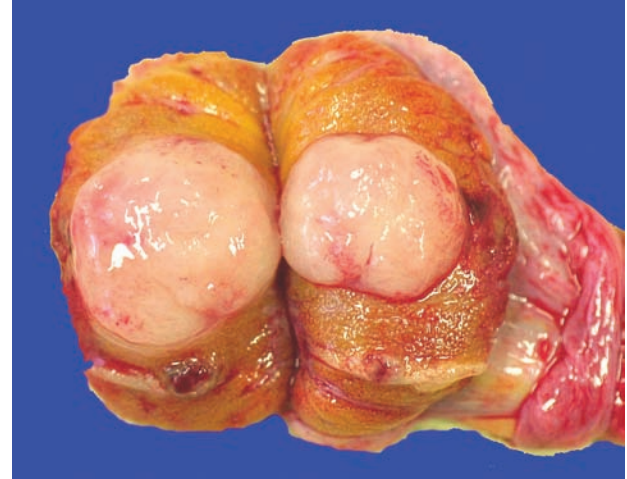
Figure 6.6
Typical gross appearance of a classical seminoma.

tumors caseous appearing necrosis may occur. Hemorrhage is not frequent and can indicate the presence of a non-seminomatous tumor component. Small hemorrhagic spots are very characteristic of seminoma with syncytiotrophoblastic giant cells. A thorough gross inspection and an abundant sampling of tumor tissue are of paramount importance, because the exclusion of non-seminomatous tumor components is mandatory for a correct therapy.

Seminoma cells are rather uniform with a rounded shape and a mostly clear, glycogen-(PAS-positive) and lipid-rich cytoplasm (Figure 6.7). Ultrastructurally they strongly resemble spermatogonia. The clear cytoplasm sharply contrasts with the distinct cell membrane which outlines the cell contours. In 87% of cases more than one mitotic figure per high power field can be seen.[62] The cytomorphology of seminoma cells strongly depends on the proper fixation of the surgical specimens. In badly fixed autolytic tissue the cytoplasm of the tumor cells becomes dark, eosinophilic, and the nuclei may swell or shrink. *The consequences are diagnostic difficulties and, in the worst case, the tumor can be mistaken for an embryonal carcinoma with, as a consequence, utterly different and inadequate therapy.*

In 'classical' seminomas tumor cells typically grow in cords and/or nests separated by more or less delicate trabeculae. In some cases, however, small nests of tumor cells are surrounded by abundant fibrotic tissue. Lymphocytic infiltration of tumor stroma is a typical feature of about 90% of seminomas[60] and can be used as a diagnostic criterion in poorly preserved, improperly processed surgical specimens.

The amount of lymphatic infiltration varies from some few lymphocytes to heavy infiltration and formation of lymphoid follicles (Figure 6.8). Furthermore, in about one-third of seminomas, tuberculoid granulomas also develop (Figure 6.9).[60] Lymphocytic infiltrates probably represent a true immunologic reaction directed against the tumor. In fact, in old series, observed before the introduction of new therapy protocoling, lymphocyte rich seminomas

Table 6.9 Relative frequency of the different testicular tumors

	Overall (%)	Prepubertal (%)
Germ cell tumors	85–90	
Seminoma	46–53	
Spermatocytic seminoma	0.5–2	
NSGCT pure forms	15–18	
Embryonal carcinoma	2–10	
Yolk sac tumor	0.3–2	15
Choriocarcinoma	0.2	
Teratoma	3–7	48
Epidermoid cyst	1	14
NSGCT mixed forms	30–33	
EC + T	9–10	
S + T	2	
S + EC + T	2–4	
CC + T	0.3	
CC + EC + T	2–4	
CC + EC + T + S	0.3–0.6	
CC + EC	1–2	
Sex cord/stromal tumors	3–5	13
Gonadoblastoma	1	2
Malignant lymphoma	6–8	4
Others & paratesticular	6–8	3
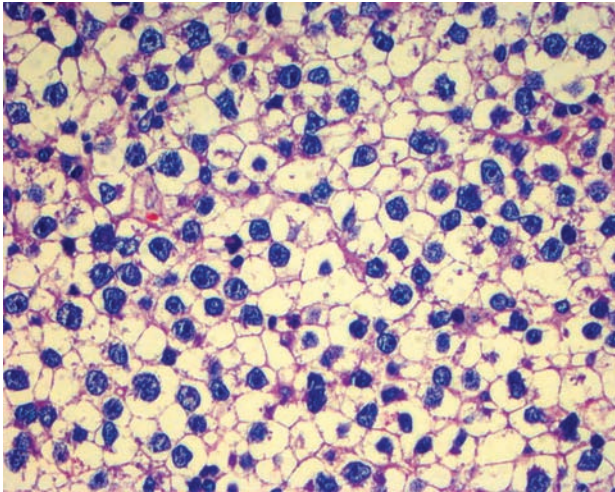
Figure 6.7
Seminoma cells with a uniform rounded shape and a mostly clear, glycogen- and lipid-rich cytoplasm.

Table 6.10 Different histologic variants of seminoma

- Intratubular seminoma
- Interstitial seminoma
- Tubular seminoma
- Pseudoglandular seminoma
- Microcystic seminoma
- Cribriform seminoma
- Seminoma with high mitotic rate
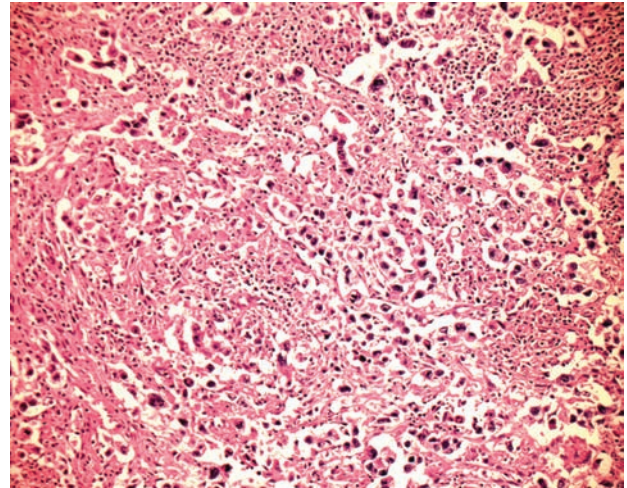
Figure 6.9
So-called granulomatous seminoma: scanty tumor cells are surrounded by proliferating fibrohistiocytic tissue.

Figure 6.8
Seminoma with marked lymphocytic infiltration.
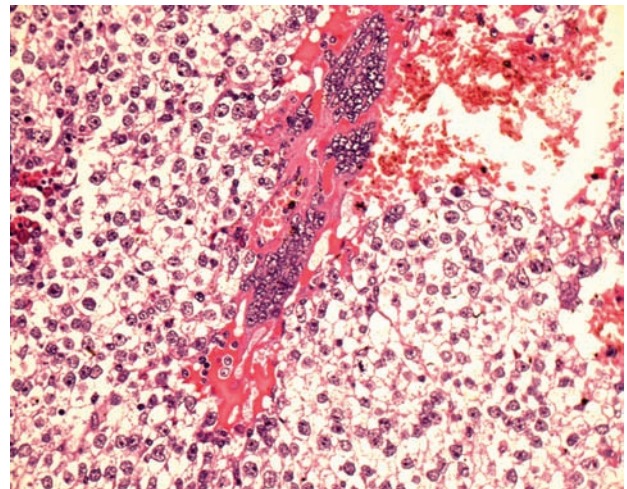
Figure 6.10
Seminoma with ßhCG-producing syncytiotrophoblastic giant cells.

did significantly better than those without lymphocytes.[60] Whether such an immunologic reaction can locally destroy the tumor is a matter of speculation.

The unofficial adjective 'classical' is meant to emphasize that the vast majority of seminomas have the above mentioned appearance. Some few, however, differ in the cytomorphology or in their growth pattern[63,64] (Table 6.10).

Seminoma with syncytiotrophoblastic cells (Figure 6.10) is the only variant listed in the WHO classification.[2] Using simple staining techniques (H&E) multinucleated giant cells are detected in about 7% of seminomas, mostly in the surroundings of vessels. With the use of antibodies against hCG, however, positive cells are present in about one-quarter of all cases.[65] Such cells also appear in other NSGCTs and must not be confused with true choriocarcinomas.

In *pseudoglandular and tubular seminoma* (Figure 6.11) tumor cells form small gland-like clefts. Accumulation of edematous fluid

in interstitial tissue gives the tumor a *microcystic* or *cribriform* (seminoma) appearance (Figure 6.12). The name *intratubular* or *interstitial seminoma* derives from the predominant way the tumor cells spread.
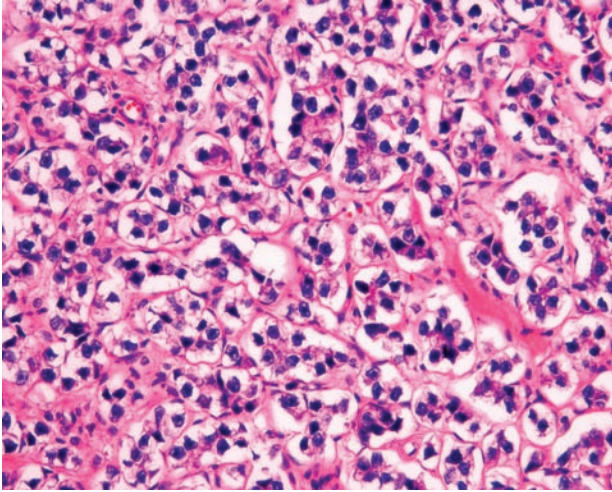
Figure 6.11
Tumor cells form gland-like clefts in tubular seminoma.
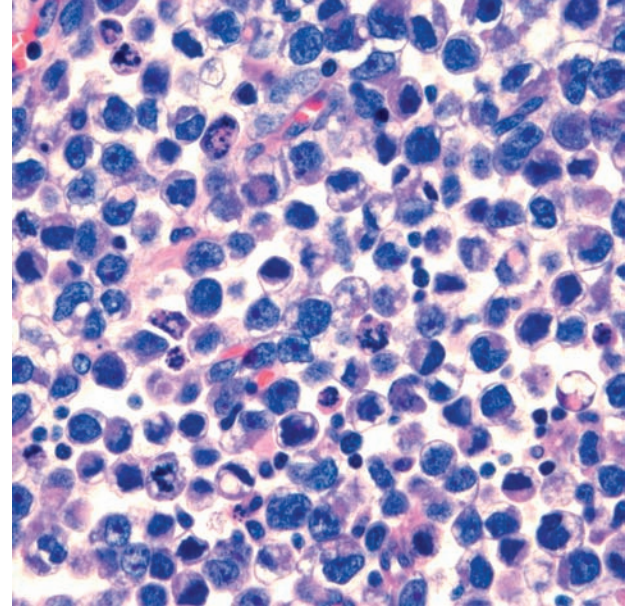
Figure 6.13
The so-called 'anaplastic seminoma' rich in mitoses and apoptosis.
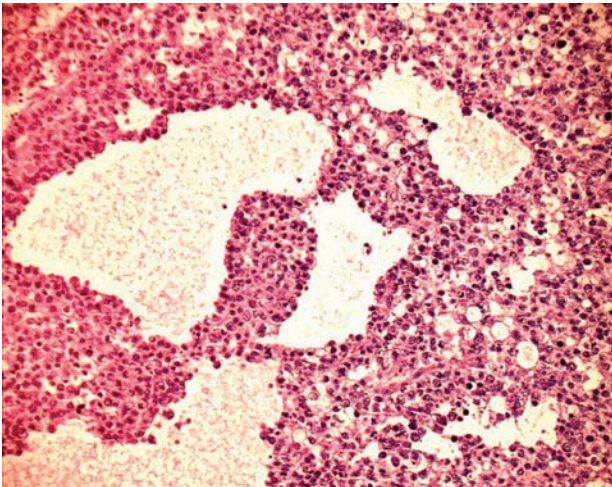
Figure 6.12
Accumulation of edema fluid in interstitium gives the seminoma a microcystic appearance.

The formerly *anaplastic* or *atypical* seminomas have been renamed as seminomas *with high mitotic rate,* which is indeed more appropriate because the degree of cellular anaplasia is not higher than in the classical type (Figure 6.13). High proliferative activity measured by counting mitoses or cells positive for proliferation markers (Ki 67) does not, however, negatively influence the course of the disease.[66,67] It is therefore highly questionable whether this kind of seminoma deserves to be considered a distinct entity.

Immunohistochemically, seminoma cells react with many different antibodies.[68] For diagnostic purposes, however, only a few are really important (Table 6.11). The most frequent and dangerous misdiagnosis is to confound seminoma with embryonal carcinoma, which usually happens when the surgical specimen is improperly fixed. Seminoma cells stain with c-Kit (CD 117) and do not react with CD 30 antibodies, whereas the cells of embryonal carcinoma behave in the opposite way – they are c-Kit-negative and CD30-positive. In some few seminomas, single tumor cells are cytokeratin- and CD 30-positive,[69] perhaps a sign of a transition beginning from seminoma to embryonal carcinoma. Rarely, these tumors are mistaken for lymphomas, which spread interstitially among the entrapped, atrophic seminiferous tubules.

Table 6.11 Immunoreactivity (%) of different TGCTs with the routinely used antibodies

	PlAP	CD117	CAM 5.2	CD30	EMA	α-FP	ß-hCG	Inhibin
IGCNU	70–100	70–100		<10		Ø		
Seminoma	70–100	70–100	<10	<10	<10	Ø		Ø
Embryonal carcinoma	70–100	Ø	100	100	<10	40–70		Ø
Yolk sac tumor	40–70	70–100	100	<10	<10	70–100	Ø	Ø
Choriocarcinoma	40–70		100	Ø	40–70	Ø	100	70–100
Single SYCT giant cells in seminoma or EC			100		40–70	Ø	100	100
Spermatocytic seminoma	Ø	Dot like	Dot like	Ø		Ø		
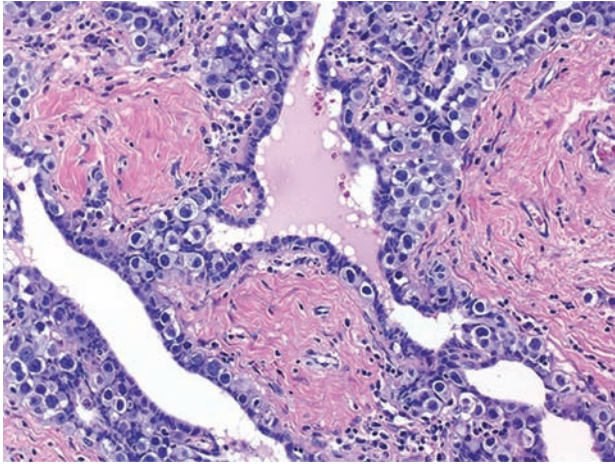
Figure 6.14
Seminoma cells with clear cytoplasm infiltrate among the rete testis epithelia.

Table 6.12 Unfavorable prognostic factors in seminoma (predictors of metastases)	
▪ Diameter > 40 mm	strong evidence
▪ Invasion of rete testis	strong evidence
▪ Age < 30 years	equivocal
▪ Vascular invasion	equivocal

as in NSGCT.[73,74] Moreover, patients younger than 34 years have a higher risk of relapse or metastases.[73,75] The initially proposed 6 cm cut-off value for the diameter of seminoma was reduced in later studies to 4 cm.[74,76,77] The 5-year relapse-free rate is 86%, 70%, and 50% for patients with no adverse prognostic factors, one risk factor, and two risk factors, respectively.[74] The prognostic importance of the presence of lymphocytes in tumor tissue has not been confirmed by recent studies.[75]

Cytogenetics

Seminomas are, without exception, aneuploid tumors.[70] As already mentioned i(12p) is present, however the number of copies is lower than in NSGCT.[71] Gain of chromosomes 7, 8, 12, 21, and X and loss of 11, 13, 18, and Y are typical.[72]

Tumor spread

The 'pagetoid' infiltration of the rete testis is not only very characteristic but also an important negative prognostic factor (Figure 6.14). The direct spread to the epididymis and spermatic cord is seldom observed nowadays but can obviously occur.

Lymphatic spread involves first the ipsilateral iliac and the para-aortic lymph nodes up to the renal arteries. Left-sided tumors can spread to the lymph nodes below the left renal vein where the left spermatic vein terminates. Later on, thoracic and even supraclavicular (Virchow's gland), auxillary, and cervical glands can be affected. Lymph node metastases in the inguinal area are encountered together with the involvement of the scrotum.

Lung and liver are the common sites of blood-borne metastases in about one-half of the cases, followed by kidney and adrenals. Even bone metastases in the femur, humerus, and spine have been observed.[60] Such metastases are, however, extremely rare and appear after the lymph node involvement. *Widespread metastatic disease or early appearing hematogenous metastases are not typical for seminomas but for NSGCTs. The possibility that due to an insufficient sampling of tumor tissue a combined tumor has been overlooked should be considered.*

Prognostic factors

The most important negative prognostic factors are the diameter of the tumor and the invasion of the rete testis (Table 6.12), whereas vascular invasion seems not to have the same prognostic importance

Clinical features

In patients with seminoma, as in other TGCTs, the main symptom is a painless hard swelling within the testis. Only 10–20% have limited pain and 6% have gynecomastia.[78] The tumor can be accompanied by hydrocele. The confirmatory ultrasound investigation significantly reduced the delay in diagnosis which is, however, sometimes caused by a patient's embarrassment.[9,78]

Lactate dehydrogenase (LDH) is a not very specific but positive tumor marker. Human chorionic gonadotropin (hCG) can be detected in the serum of patients with seminoma with syncytiotrophoblastic cells. Alphafetoprotein (AFP) is not secreted by seminomas. Elevated AFP in the serum of patients with histologically proven seminoma means, therefore, that a combined tumor (seminoma + NSGCT) has been overlooked because of inadequate sampling, but a laboratory error of AFP measurement can also cause confusion. In such cases both pathology and laboratory results should be revised.

Of stage I seminomas, 99% are cured. After orchidectomy the policy of surveillance with a relapse risk of 5–21% can be adopted. Traditionally, however, the retroperitoneal and ipsilateral lymph nodes are treated with radiotherapy (20 Gy in 10 fractions).[9] Patients with relapse after radiotherapy (<5%) can be successfully cured by chemotherapy. Instead of radiotherapy some centers prefer adjuvant carboplatin chemotherapy with an actuarial 5-year disease-free survival rate of 96.2%.[77]

Between 15 and 20% of seminoma patients presenting with retroperitoneal lymphadenopathy (stage II) need radiotherapy or, alternatively, carboplatin followed by chemotherapy.[79] The actuarial 5-year disease-free survival rate is 96.2%.[9] Even in advanced metastatic seminoma a cure rate of 90% can be reached using the standard combined bleomycin, etopside, and cisplatin (BEP) regimen.[9]

Spermatocytic seminoma

Spermatocytic seminoma first described by Masson in 1946[80] is a peculiar and fascinating germ cell tumor which arises only in the male gonad. In spite of some morphologic similarities it is not a

variant of the classic seminoma, having a different and practically unknown oncogenesis and a completely different clinical course.

Epidemiology

Although a distinct entity, the incidence is still measured in relation to seminoma – in various series spermatocytic seminoma represent 1–4%[81–83] of seminomas, that is, about 0.5–1% of all TGCTs. Patients are consistently older (average 52 years) than those with other types of TGCTs (Table 6.13), but some few cases have also been observed in younger men.[82,84] Asynchronous bilateral occurrence is also more frequent (9%) than in other TGCTs.[82] There are no racial differences and no causal relationships with cryptorchidism.[85]

Morphology

The appearance to the naked eye is quite different from classic seminoma: the cut surface is described as mucoid, edematous, or gelatinous (Figure 6.15). Cystic, necrotic, and even hemorrhagic areas may be present. The tumor tissue is cream-colored or yellowish. The tumor is well circumscribed and can be multinodular. Also, microscopically the tumor borders are sharp (Figure 6.16). The tumor grows in an expansive and not infiltrative manner.

Microscopically, the tumor cells somehow mimic the different stages of spermatogenesis because of three different tumor cell types (Figure 6.17). The large (Ø = 15–20 μm) cells with rather regular round nucleus predominate. The small cells (Ø = 6–8 μm) resemble lymphocytes and the single scattered giant cells (Ø = 50–150 μm) have nuclei with a coarse chromatin, which can be compared with the spirem of the meiotic division of the spermatocytes.[86] Lymphocytes are scanty and in the neighboring tubules atypical germ cells (IGCNUs) are missed, but intratubular spread of tumor cells is very common (Figure 6.18). The polymorphous micromorphology with many mitotic figures gives the impression of an extremely aggressive tumor. The so-called anaplastic spermatocytic seminoma contains a monomorphous population of large cells with big nucleoli.[87]

Table 6.13 Differences between classical and spermatocytic seminoma

	Seminoma	Spermatocytic seminoma
Patient's age (years)	35–40	50–58
Bilateral (%)	2	9
Extragonadal location	Occasionally	Never
History of cryptorchidism	Yes	No
Gross	Solid, firm	Mucoid, gelatinous
Cytomorphology	Monomorphous cells, Ø = 15–25 μm	3 different cell types: small Ø = 6–8 μm intermediate Ø = 15–20 μm to giant Ø = 50–150 μm
Lymphocytes	Common & abundant	Absent
Accompanying IGCNU	>90%	Absent

Figure 6.15
Spermatocytic seminoma with a typical central gelatinous area.
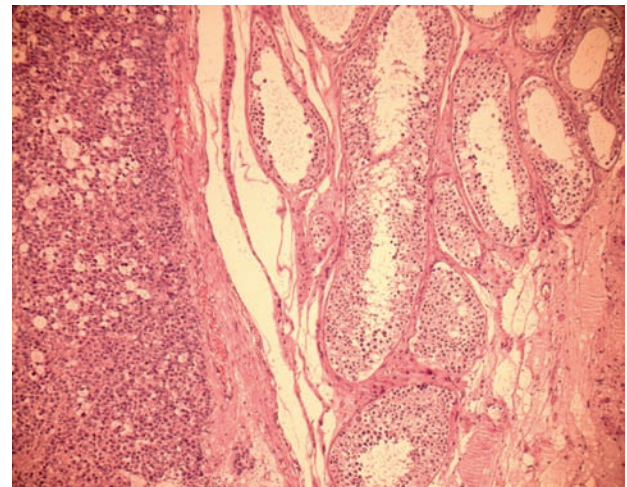
Figure 6.16
Expansive growth of spermatocytic seminoma. Note the sharp interface between tumor and adjacent parenchyma.
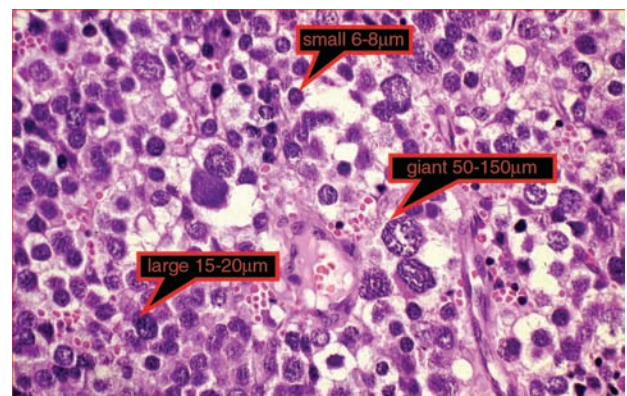
Figure 6.17
The very charateristic cytology of spermatocytic seminoma with three different tumor cell types.

Immunohistochemically (Table 6.12) the tumor cells are negative for all markers which are commonly found in TGCTs. The PlAP reaction is, with very few exceptions, negative.[85] Forty percent of spermatocytic seminomas react positively with c-kit (CD117) antibodies and some few show a dot-like perinuclear reaction for low-molecular-weight cytokeratin (CAM 5.2).[88,89]

In our experience, spermatocytic seminoma, due to its rarity, is one of the most frequently misdiagnosed tumors. The spectrum of wrong diagnoses ranges from anaplastic seminoma to malignant lymphoma. The wrong diagnosis implies an unnecessary therapy.

Some dozen cases of spermatocytic seminoma combined with sarcoma, mostly rhabdomyosarcoma, have been described.[82,85] The histogenesis of these variants is completely unknown.

Cytogenetics

The tumor cells are mostly polyploid or aneuploid. The frequent alterations of the number of chromosome copies are gains of chromosomes 1, 9, 18, 20, and X and losses of 7, 15, and 16 or 16p (Figure 6.19). However only gain of chromosomes 9 and X are found in all investigated spermatocytic seminoma. Gain of chromosome 9 combined with an unchanged chromosome 12 seems to be specific for this tumor.[84]

Tumor spread

Usually these tumors are confined to the testis and never metastasize in distant organs. Thus far, only two cases of spermatocytic seminomas with retroperitoneal lymph node metastases have been reported.[84,90] The sarcoma component in combined tumors obviously metastasizes, primarily to the lung.

Clinical features

Patients do not have a history of cryptorchidism. Painless testicular swelling is the leading symptom. Postoperative treatment can be omitted in favour of surveillance because relapses have never been observed.[91] Spermatocytic seminomas combined with sarcoma kill patients with few exceptions within 2 years.[2]

Figure 6.18
Intratubular spread of spermatocytic seminoma.
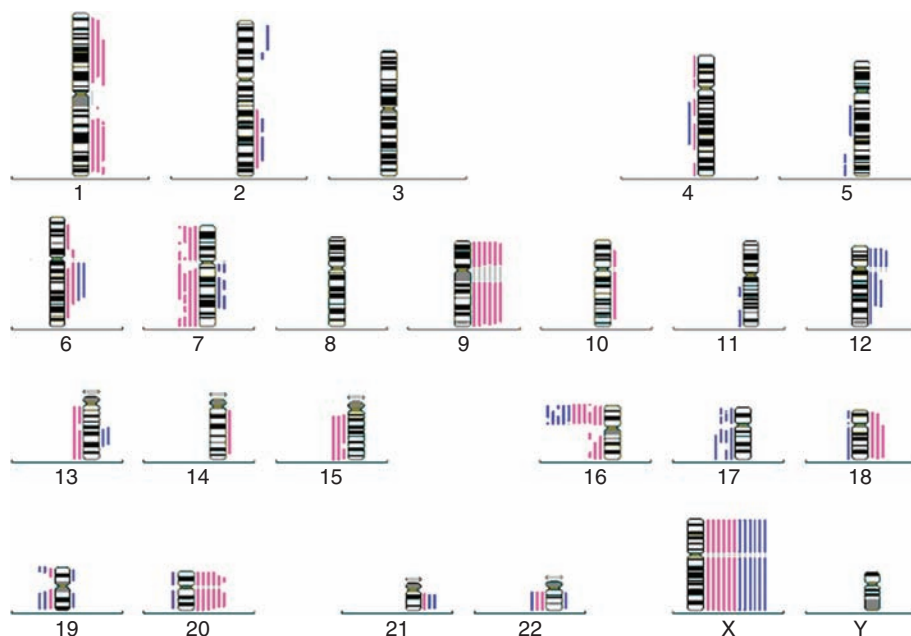
Figure 6.19
Cytogenetic differences between classical (blue bars) and spermatocytic seminoma (red bars). Bars on the right side of the chromosome mean gains, and on the left side losses of entire chromosomes or of part of them. The gain of chromosome 9 is very specific for spermatocytic seminoma.

Part 4

Non seminomatous and mixed germ cell tumors

NSGCTs have a completely different biology and clinical course from seminomas. The majority shows not a single histologic type (pure form) but a mixture of different germ cell tumor types. Morphologic prognostic factors strongly depend on the presence and amount of single tumor components; tumor spread and therapy are more or less the same for all NSGCTs. (For that reason, these items will be presented together for all tumor types at the end of the chapter.)

Embryonal carcinoma

Malignant teratoma undifferentiated (British classification)

Epidemiology

The pure form of embryonal carcinoma (EC) accounts only for 2–10% of all TGCTs, but is very frequent (80%) in mixed neoplasms with more than one germ cell component. The patients are on average 30 years old, that is, nearly as old as those with seminoma. Its appearance in childhood and after age 50 is a rarity (Table 6.7).

Morphology

The tumors are usually small and the cut surface is granular. Necroses and small hemorrhagic spots give the grayish colored tumor a variegated appearance (Figure 6.20). The growth pattern can be solid, papillar, glandular, or tubular. Intratubular spreading tumor masses with central necrosis resemble comedo carcinomas. The tumor cells are large primitive epithelial cells with a cytoplasm varying from amphophilic to basophilic or clear (Figures 6.21 and 6.22). The large pleomorphic and hyperchromatic nuclei contain one or more large eosinophilic nucleoli. Mitoses are abundant. In some cases syncytiotrophoblastic giant cells are present. Vascular invasion (Figure 6.23) is easily detected in more than half the cases.[92]
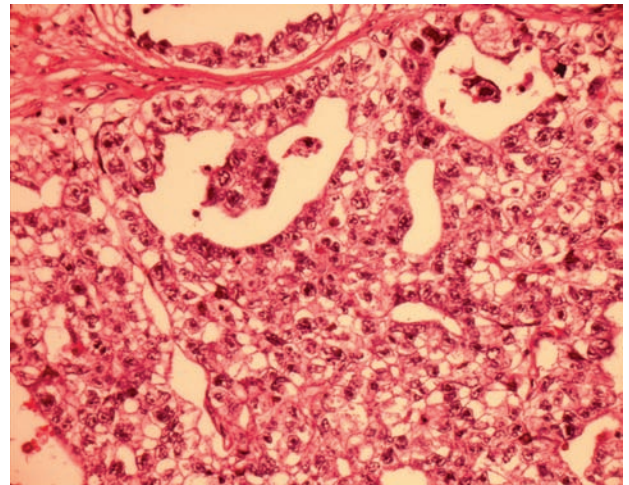
Figure 6.21
Embryonal carcinoma cells are somewhat larger and more polymorphous than seminoma cells.

Figure 6.22
Intratubular comedo-like spread of embryonal carcinoma.

Figure 6.20
Gross appearance of embryonal carcinoma with central necrosis.
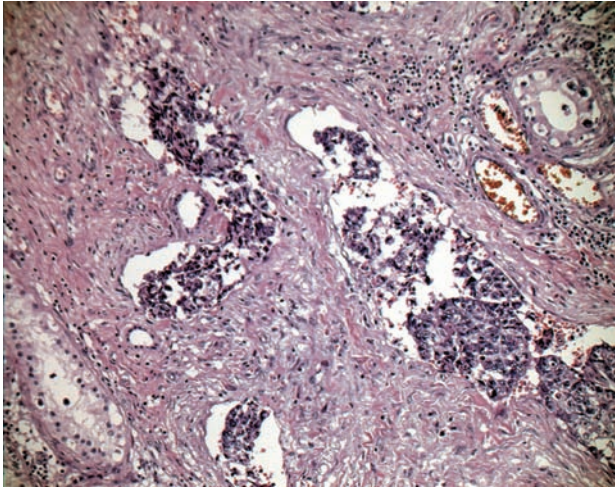
Figure 6.23
Intravascular embryonal carcinoma cells are a very significant predictive factor of unfavorable prognosis (70% lymph node metastases).
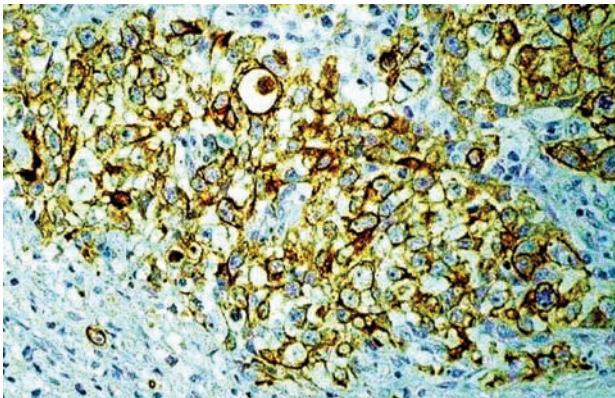
Figure 6.24
Positive immunohistochemical reaction of embryonal carcinoma cells with CD 30 (Ki 1).

The positive staining with polyclonal cytokeratin antibodies (AE1/AE3; CAM 5.2) confirms the epithelial nature of these tumor cells (Table 6.11). Unlike with seminomas, the PlAP reaction is only focally positive. The strong and specific staining with CD 30 (Ki 1, Ber-H2) can lead to a wrong diagnosis of giant cell (immunoblastic) lymphoma (Figure 6.24). As already mentioned, ECs are negative for c-kit (CD 117), whereas seminomas do not react with cytokeratin antibodies and CD 30.

Cytogenetics

The anuploid or even triploid tumor cells show manifold chromosomal aberrations, most constant being the presence of isochromosome 12. The number of i(12p) copies seems to correlate with the aggressiveness of the EC.[93]

Clinical features

The leading symptom is a testicular mass which, contrary to seminoma, causes pain and discomfort in about 30% of patients.[94] Ten percent suffer from systemic symptoms such as weight loss, fever, night sweats, and headaches, or have brain or lung metastases. Alfafetoprotein (AFP) in serum can be elevated even in histologically pure EC, and hCG can be detected in cases with syncytiotrophoblastic giant cells.[95] Less than half the patients with NSGCT present a localized disease, 40% have retroperitoneal lymph node involvement, and 20% supradiaphragmal lymph nodes and/or visceral metastases.[96] Pure EC is an extremely aggressive tumor; nevertheless, it can be cured with modern therapy protocols.

Yolk sac tumor

Orchioblastoma (British classification)   **Endodermal sinus tumor** (Teilum)[97]

Epidemiology

The pure form of yolk sac tumor (YST) is the most frequent (80%) TGCT of childhood.[98] The average patient age is about 18 months, since most tumors arise in the first 2 years of life. In adults, YST is a frequent (40%) component of mixed TGCT, but occurs rarely in pure form. The epidemiologic data about possible racial preferences are contradictory. In some reports the incidence is equal in black and white children, whereas in other reports, it is just as with adults, namely, white children and Indians prevail.[2] All these epidemiologic studies are, however, biased because of the small number of cases.

Morphology

Typically, the tumor is not encapsulated and is yellow or white in color. Tissue consistency is usually soft, but can also be firm. Cystic changes are common (Figure 6.25). Necroses and hemorrhages are present, especially in large tumors of adults.

At first glance, the microscopic impression is that of a confusing variety of cells and patterns, but in sporadic cases the tumor is composed of one single cell type or only one histologic pattern. Microcystic, papillary, and solid, spindle cell, and mucoid areas can
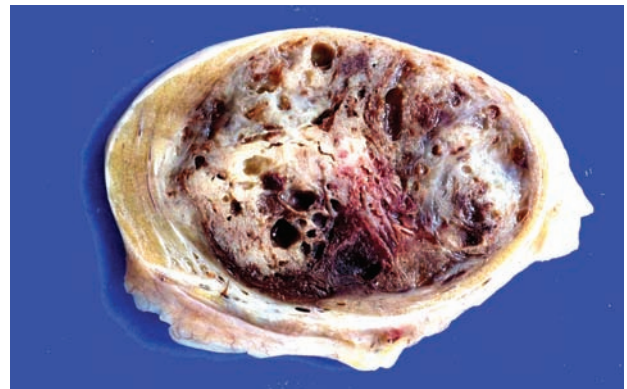
Figure 6.25
Multiple small cysts on the cut surface of a yolk sac tumor.

alternate in the different parts of the tumor and produce a mesh-work with spaces appearing to be empty or glandular and pseudo-glandular structures (Figures 6.26 and 6.27). The eponymous structures resembling yolk sac (vitelline) are not always present. The very characteristic Schiller–Duval (Figure 6.28) bodies are an imitation of the endoderm with cuboidal cells covering a vascularized stalk of connective tissue. The similarity of the tumor cells to primitive enterocytes is clearly seen in an electron microscope, showing cells with microvilli on the surface. Tumor cells can contain hyaline globules ($\varnothing \leq 1$ μm) staining positively with PAS (diastase-resistant), which are found only in this TGCT (Figure 6.29). The 11 different microscopic patterns described thus far (Table 6.14) lack any clinical importance and are also of questionable diagnostic value, because they are often present only in small tumor areas.

Figure 6.28
Schiller–Duval bodies in a yolk sac tumor.

Figure 6.26
Microcystic type of yolk sac tumor.
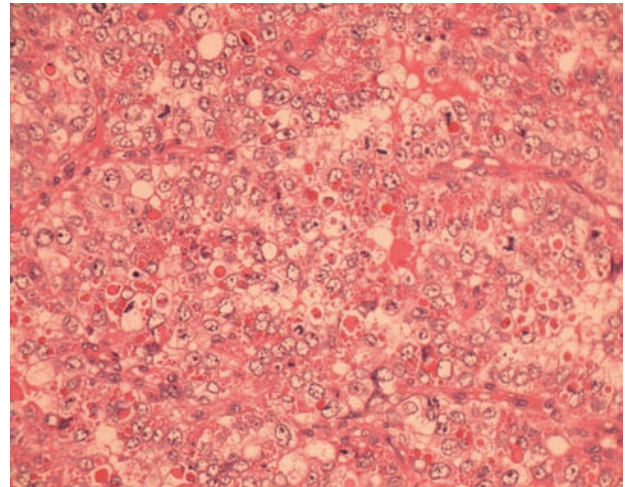
Figure 6.29
Typical intracellular globules in a yolk sac tumor.

Table 6.14 Histologic pattern of yolk sac tumor
■ Microcystic – reticular
■ Macrocystic
■ Endodermal sinus
■ Papillary
■ Solid pattern
■ Glandular – alveolar
■ Myxomatous
■ Sarcomatoid – spindle cell
■ Vitelline
■ Hepatoid
■ Parietal

Figure 6.27
Papillary type of yolk sac tumor.

Experienced pathologists do not have any problem with the diagnosis. In adult patients, in whom pure forms of YST are rare, confusion with embryonal carcinoma and rarely with seminoma can arise, especially if the tumor is completely solid-structured. (However,

only the misdiagnosis seminoma has negative consequences, because of a completely different therapy.)

Immunohistochemically all tumor cells react strongly positive with cytokeratin antibodies, and, unlike embryonal carcinoma, negatively with CD 30.[95,99] Even when these tumor cells are the typical producer of AFP, not all tumors are positive (74–100%), and in children completely negative tumors can be observed. The immunohistochemical reaction is usually patchy, not found in all tumor cells and not in all areas. To avoid wrong diagnosis, a generous sampling is advisable; also because AFP-positive tumor cells are encountered in one-third of embryonal carcinomas.

Cytogenetics

Loss of 1p and 6q is rather typical for infantile YST.[100] Other anomalies have been sporadically observed, but genes somehow involved in the oncogenesis are not yet known.

Clinical features

As in all testicular tumors the asymptomatic scrotal mass is the leading symptom. AFP in serum is elevated in 90% of cases.[101] Tumor spread and therapy in adults follow the pattern of all NSGCTs (see Chapter). In infants a wait-and-see stance can be adopted, because positive retroperitoneal lymph nodes are observed in 4–14% of cases.[102] More recent studies[103] do not confirm the old supposition that children under age 2 have a better prognosis than older ones.

Polyembryoma

This tumor never occurs in pure form and invariably represents only a microscopically detectable structure, which is part of a NSGCT – most commonly of a teratoma. The structure called 'embryoid body' roughly resembles a presomitic embryo of about 14 days old (Figure 6.30). The 'embryoid bodies' are embedded in a myxomatous stroma and are scattered among other components of NSGCT.

Choriocarcinoma and other throphoblastic neoplasia

Malignant teratoma throphoblastic type [British classification]

Epidemiology

Choriocarcinomas are the rarest TGCT with an incidence of about $0.8/10^5$. The pure form accounts for less than 0.2% of all TGCTs. The patients are rather young, with a peak between 25 and 30 years.

Morphology

Grossly the tumor is a small, hemorrhagic nodule sometimes surrounded by a rim of whitish preserved tumor tissue. The tumor consists of three cellular components: the cytotrophoblast, the intermediate trophoblast, and the syncytiotrophoblastic giant cells (Figure 6.31). The leading cell is the small rounded cytotrophoblast with water-clear cytoplasm (Figure 6.32). Such cells with more
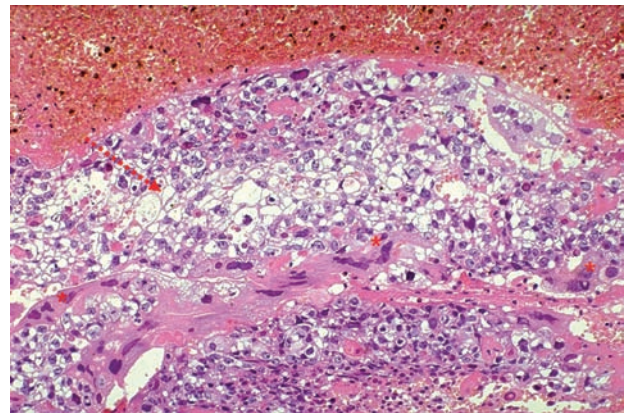
Figure 6.31
Overview of a choriocarcinoma.

Figure 6.30
Embryoid bodies in polyembryoma resemble a presomitic embryo around 14 days old.
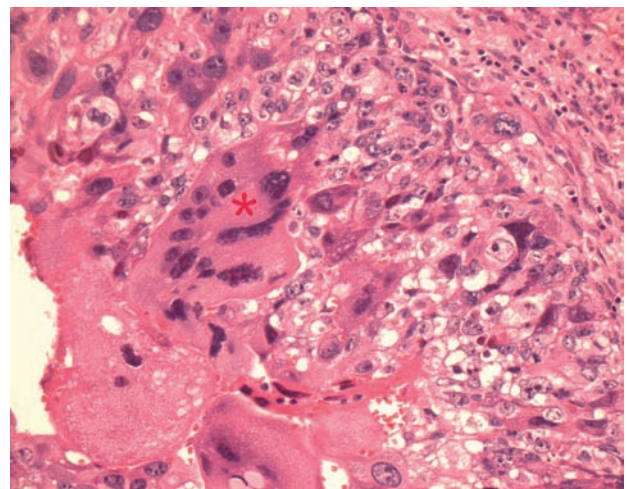
Figure 6.32
Cytotrophoblast cells with clear cytoplasm are covered by typical syncytiotrophoblast giant cells.
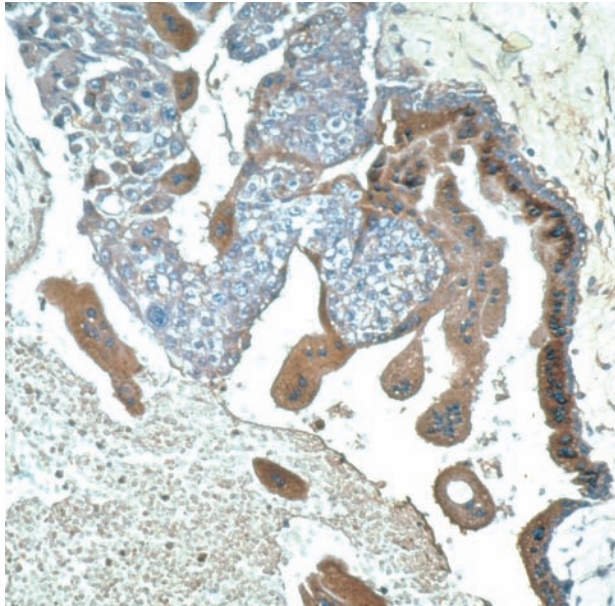
Figure 6.33
Positive immunohistochemical reaction of the syncytiotrophoblastic giant cells with ßhCG antibodies. The cytotrophoblast does not produce this hormone and is unstained.

eosinophilic cytoplasm are supposed to be the 'intermediate trophoblast'. The syncytiotrophoblastic giant cells lie on the surface of the cytotrophoblast. The tumor masses are surrounded by blood and are located close to small vessels.

Monophasic choriocarcinoma is the term used for such tumors composed only of cytotrophoblasts and lacking the syncytiotrophoblastic giant cells. Tumors made out of solely intermediate cytotrophoblasts are called, as in the uterus, *placental site trophoblastic tumor* [ICD-O 9084]. Thus far, only one monophasic and two placental site tumors have been described.[104,105]

All types of cytotrophoblast react immunohistochemically with cytokeratin antibodies (CK 7, 8, 18, 19, CAM5.2, AE1: AE3) as well as with human placental lactogen (hPL). Syncytiotrophoblastic giant cells obviously react strongly positive with βhCG antibodies (Figure 6.33), and also express epithelial membrane antigen (EMA) and the alfa subunit of inhibin.

Caveat: the diagnosis of choriocarcinoma is based on the identification of both trophoblast types (cyto- and syncytiotrophoblast). hCG-positive syncytiotrophoblastic giant cells alone do not permit the diagnosis of choriocarcinoma, because they are also found in classical seminomas as well as all other NSGCTs.

Hemorrhages due to other causes (coagulopathy, torsio, and trauma) also cause testicular swelling and tissue necrosis which can mislead to a tragic diagnostic error.

Cytogenetic

To date, no studies on testicular choriocarcinoma have been carried out. In females, a few analyses have been done without finding specific chromosomal aberrations. Tumor cells of postgestational choriocarcinomas such as partial hydatidiform mole are triploid.[106] One ovarian choriocarcinoma of germ cell origin exhibited the typical i(12p).[107]

Clinical features

Choriocarcinoma is a highly aggressive neoplasm with approximately 70% of patients having metastatic disease at the time of diagnosis. Primary symptoms are caused mostly by blood-borne metastases which are located in the lung (100%), liver (86%), gastrointestinal tract (71%), and brain (56%), whereas the retroperitoneal lymph nodes are not involved. The high hCG levels in serum (>100 000 IU/l) can cause a gynecomastia (10%) and in a few cases also a thyrotoxic crisis due to a cross-reaction of hCG with TSH.[108] Standard treatment is orchiectomy and cyclical POMB/ACE chemotherapy.[109] Response to therapy is signaled by reduction of tumor volume and falling hCG, whereas persistence of elevated hCG means residual tumor and worse prognosis. Of patients with metastases, 75% survive 3 years. In many cases death occurs due to hemorrhage secondary to brain and/or gastrointestinal metastases, a condition called 'choroicarcinoma syndrome'.[110]

Teratoma

Teratoma differentiated [British classification]

Epidemiology

Teratomas are, after YST, the second most frequent (14–20%) TGCT in infancy, with an average age of 20 months.[59] In adults pure teratomas account for 3–7% of TGCTs but they are a component in more than half of the mixed germ cell tumors.

Morphology

The name given to this amazing tumor by Virchow[111] derives from teras, which in ancient Greek means marvel or monster. The tumor is composed of tissue components deriving from all three germinal layers – endo-, ecto-, and mesoderm. Thus, the gross morphology depends on the distribution and amount of single tumor components. On the cut surface, glassy nodules representing cartilaginous areas (Figure 6.34, 6.35), small cysts filled either with mucus or
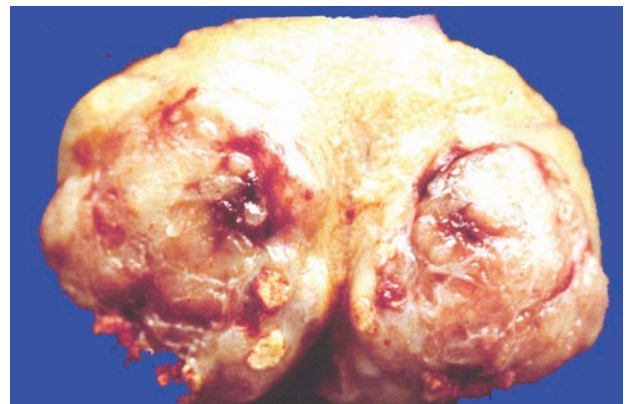
Figure 6.34
Teratoma with prominent cartilaginous areas.

Figure 6.35
Teratoma with cartilaginous areas and microcystic structure.

Figure 6.36
Cystic teratoma with necrotic and hemorrhagic areas.

Table 6.15 Differential diagnosis of cystic testicular lesions in childhood[116]
Teratoma
Epidermoid cyst
Dermoid cyst
Yolk sac tumor
Ovarian type cystadenoma
Juvenile granulosa cell tumor
Cystic lymphangioma
Cystic dysplasia of the rete testis
Simple cysts

with laminated keratin, and pigmented areas can be recognized (Figure 6.36). Compared with other TGCTs the consistency is always significantly more firm. In children the appearance is usually multicystic (Table 6.15).

Well-differentiated somatic tissue components have been classified in the past as *mature teratoma,* whereas teratomas containing normal fetal type tissue have been called *immature. The new WHO 2004*[2]

classification avoids using these two terms because they have often been erroneously interpreted as synonyms for benign and malignant, respectively. However, they only describe morphologic features and lack any prognostic significance.

Mature teratomas contain cysts lined by squamous or glandular epithelium of enteric type or ciliated respiratory type epithelium (Figure 6.37). Cysts can be filled with mucus or keratin. Organoid structures mimicking gout or bronchous are made of the corresponding epithelium encircled by smooth muscle. As in normal organs also in these organoid structures neuroendocrine cells producing all kind of hormones (gastrin, bombesin, somatostatin, etc.) are scattered[112] among the columnar epithelia (Figure 6.38).

Mesodermal tissue is always represented by smooth muscle and mostly also by hyaline cartilage; bone with or without hematopoietic marrow is less common (Figure 6.39). Neuroglia with ependymal differentiation is also a rather common component. Pigmented retinal epithelium can occasionally be seen (Figure 6.40). Differentiated liver, prostate, pancreas, and thyroid are rarities (Figure 6.41).
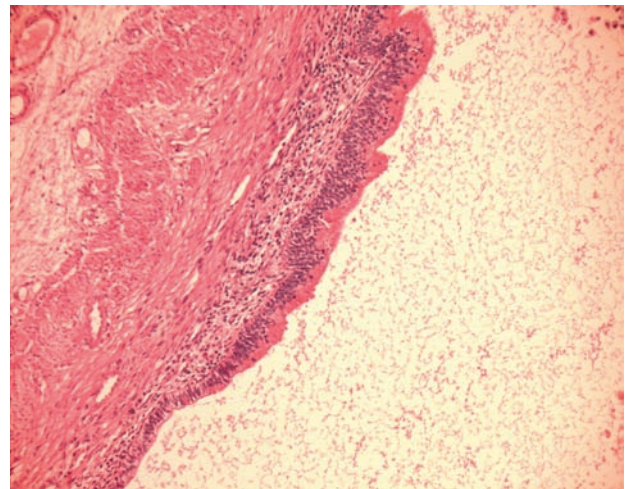
Figure 6.37
Teratoma with small lumen lined by respiratory type epithelium and smooth muscles in the wall.
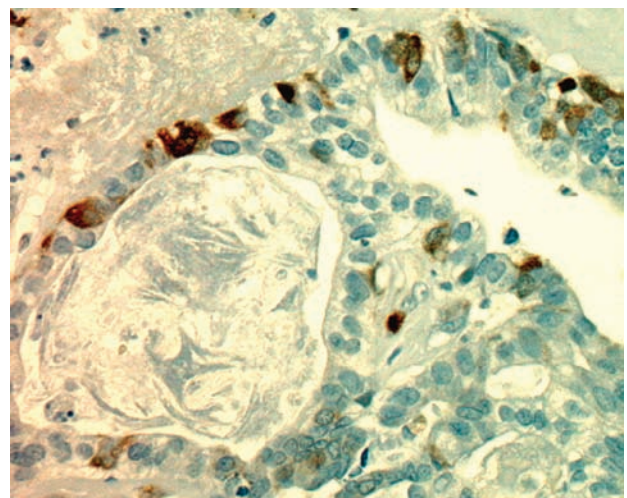
Figure 6.38
Neuroendocrine cells in gland epithelium of a teratoma.

Immature teratomas contain an undifferentiated spindle cell mesenchymal stroma and small immature glands. Also the squamous epithelium is arranged in solid nests without keratinization. Other components are primitive neuroepithelium, renal blastema resembling Wilms tumor (Figure 6.42), rhabdomyoblasts, and fetal adipose tissue with lipoblasts (Figure 6.43).

In the WHO 2004 classification[2] the *dermoid cyst [ICD-O9084]* is listed as an 'official' variant of teratoma. The tumor consists of cysts lined by epidermis with skin, hair follicle, and sebaceous glands (Figure 6.44). Other mature components can be found but their quantity is negligible.[115] This teratoma type is ordinary in the ovary but remains extremely rare in the testis, with some few cases reported.[2] Since metastases have never been described, perhaps the dermoid cyst deserves to be considered a distinct diagnostic entity.

Monodermal teratomas are those tumors in which a tissue component deriving from one germinal layer overgrows the other. The most frequent form is the primitive neuroectodermal tumor (Figure 6.45) (PNET) (Figure 6.45). Other monodermal tumors
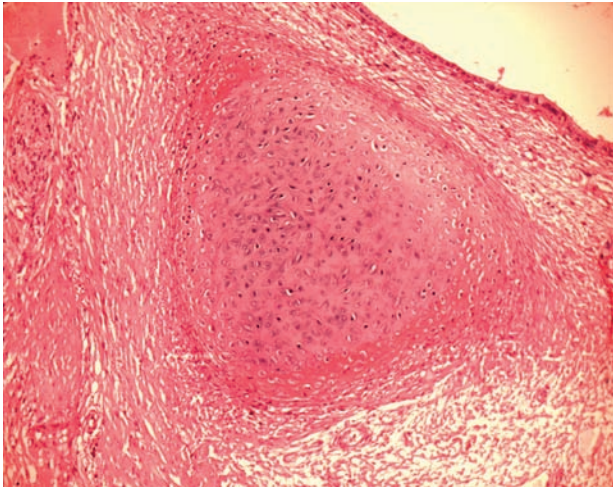
described are chondromas, Wilms tumor (nephroblastoma), and carcinoids. The last two, however, are listed again in the WHO 2004 classification in the category of 'miscellaneous tumors', which does not make much sense because the normal testis does not contain a cell from which both tumors could develop.

The most common monodermal differentiated tumor is the *epidermoid cyst* (Figure 6.46), which accounts for 1% of all intrascrotal tumors and can arise at any age.[116] They are easily recognizable by the naked eye because they have a thin whitish wall and are filled with horny material arranged in a laminated layer (onionskin-like). The cyst is lined by an epidermis-like layer of squamous epithelium (Figure 6.47). Some authors regard the cyst as a teratoma only in cases when the surrounding testicular tissue IGCNU can be identified, otherwise the cyst is considered to be a tumor-like lesion. In one case, an orchidectomy should be required; in the other, only a tumor enucleation.[117] This cavilling view is devoid of any practical or even theoretic importance because a metastasizing epidermoid cyst has never been reported. One could object that teratomas in infancy are also not accompanied by IGCNU, yet are still TGCTs.

Carcinoids arise from neuroendocrine cells which abound in teratomas[112] but do not exist in normal testicular tissue. The existence of so-called primary carcinoids without accompanying teratoma can easily be explained through the overgrowth of neurendocrine cells. The detection of teratomatous areas also depends on a very thorough sampling; thus, the existence of primary carcinoids can be called into question. In fact, 'primary' carcinoids are larger than small ones and 8% of them metastasize.[118]

If a non-germ cell tumor[119] arises from a somatic tissue component, it is classified as *teratoma with somatic type malignancy [ICD-O 9084/3]*. Such malignancies become clinically important only if the somatic malignancy fills a field of view by low magnification (4× objective). Sarcomas, in particular rhabdomyosarcoma, are the most common somatic malignancies (Figure 6.48). But primitive neuroectodermal tumors and squamous and adenocarcinomas have also been observed (Table 6.16). Somatic type differentiation is seen in 4% of patients with metastatic disease,[120] probably also induced by chemotherapy.

Teratomas are not difficult to recognize, so immunohiostochemistry is not accustomed to solving certain differential diagnostic problems. The immunophenotype of the various tissues obviously

Figure 6.39
Young partially immature cartilage in a teratoma and an adjacent gland lined by columnar epithelium.
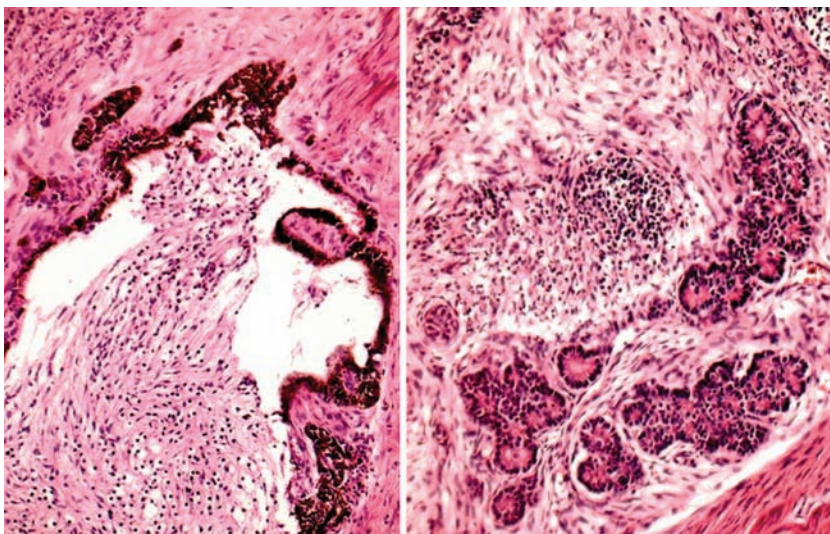
Figure 6.40
Pigmented retina-like epithelium (left) and neuroepithelium forming rosettes (right).
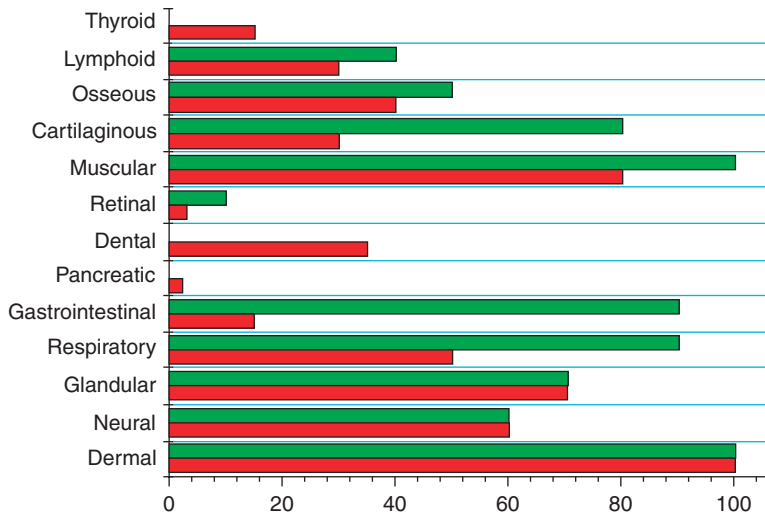
Figure 6.41
Frequency of differentiated tissue in teratomas of the testis (green bars) and ovary (red bars). In testis tumors respiratory, gastrointestinal, glandular, and dermal structures prevail. Thyroid and pancreatic tissue, rather common in teratoma of the ovaries, is not encountered in testicular teratomas. (Modified after Damjanov.[113])
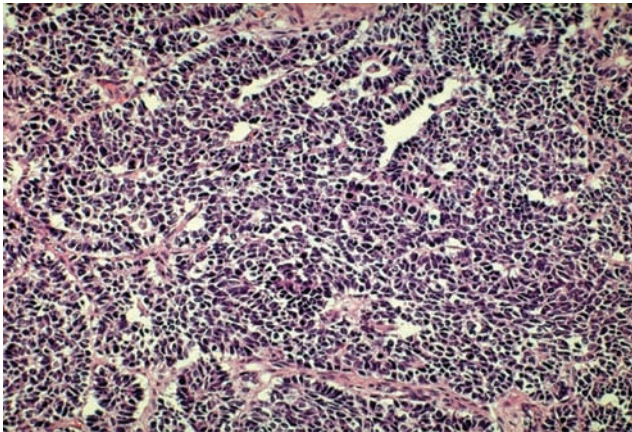
Figure 6.42
Nephroblastoma (Wilms tumor) developed in a teratoma.

Figure 6.44
Dermoid cyst lined by epidermis with skin and hair follicles.

corresponds to those of the normal cell type, with the same antibodies as their normal counterparts.

Cytogenetics

Teratomas are diploid in children and hypotriploid in adults.[121] The only specific aberration is the isochromosome i(12p). Teratomas with somatic type malignancies can show both: aberrations typical for the respective somatic tumor (mostly translocations) and simultaneously also i(12p) specific for TGCTs.[122]

Figure 6.43
Cartilage and rhabdomyoblastic differentiation in a teratoma.
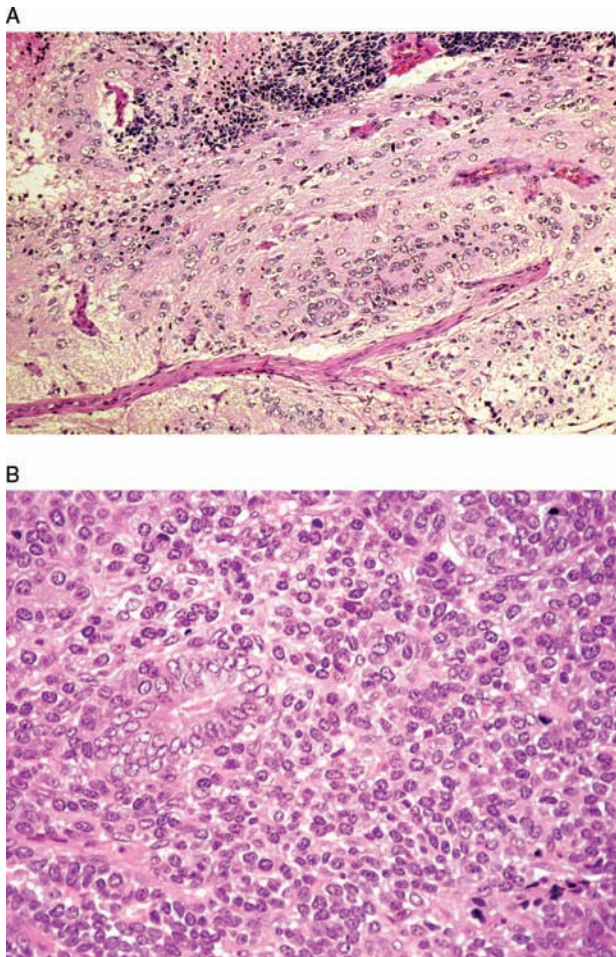
Figure 6.45

(A) Monodermal teratoma differentiation into structures of a primitive neuroectodermal tumor (PNET). The figure shows neurofilaments, ganglion cells, and small neuroblastoma-like cells (bottom). (B) Neuroepithelial differentiation (neuroepithelioma).

Figure 6.47

Epidermoid cyst lined only by squamous epithelium. Hair follicles and sebaceous glands typical for dermoid cyst are missed.

Figure 6.46

Macroscopic appearance of an epidermoid cyst with squamous material.
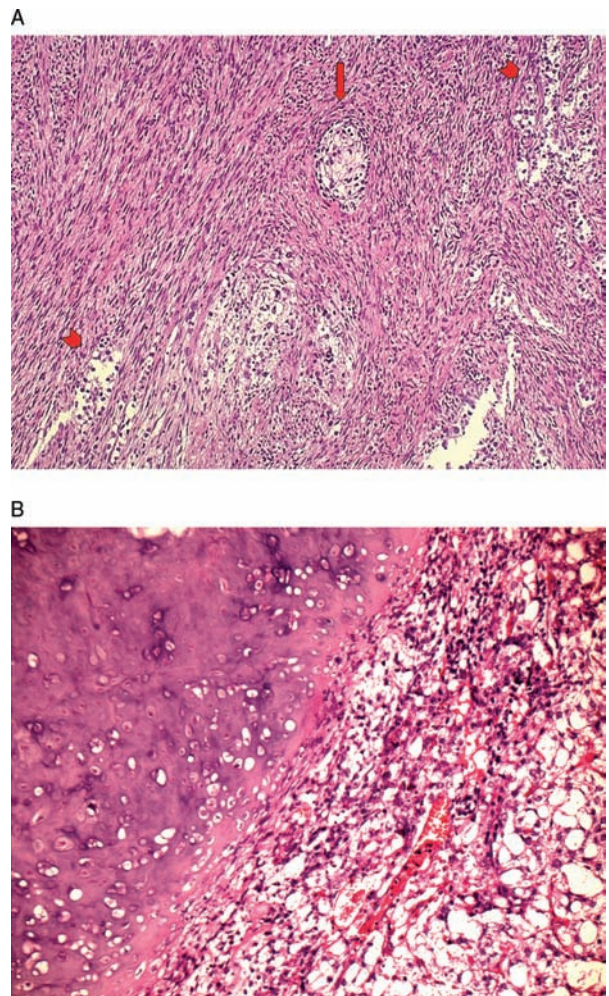
Figure 6.48

(A) Somatic-type tumor developed in teratoma. The main portion of the tumor consists of a leiomyosarcoma structure with entrapped islands of seminoma cells (arrowheads) and immature squamous epithelium (arrow). (B) Chondrosarcoma adjacent to yolk sac structures.

Table 6.16 The most frequently reported somatic type malignancies developed in teratoma

- Rhabdomyosarcoma
- PNET
- Chondrosarcoma
- Osteosarcoma
- Malignant Schwannoma
- Nephroblastoma (Wilms tumor)
- Carcinoid
- Adenocarcinoma
- Squamous carcinoma
- Neuroendocrine carcinoma

Clinical features

Testicular mass is the main symptom, but children also show typical associations with other diseases: inguinal hernia (7%), malformations of the urogenital tract (2.5%) and cryptorchidism (5%), Down syndrome (2%), Klinefelter syndrome (1.5%), xeroderma pigmentosum (0.5%), hemophilia (0.5%), and ataxia (0.5%).[123]

The tumor is absolutely benign in childhood, whereas in adults only dermoid and epidermoid cysts do not metastasize or relapse. In adults they are metastatic to the retroperitoneal lymph nodes and rather insensitive to chemo- and radiotherapy, thus necessitating resection. Somatic type malignancies arising in teratomas do not respond to the standard TGCT therapy, which should therefore be specifically tailored to the somatic tumor component.[122]

Tumors of more than one histologic type [mixed forms]

Malignant teratoma of intermediate type or combined tumor seminoma + teratoma
    [British classification]
[Teratocarcinoma of the old WHO 1976 classification]

Epidemiology

These tumors, at 30–54%, are almost as frequent as pure seminomas. In NSGCTs combined with seminoma, the average age of the patients depends interestingly on the amount of the two tumor components: patients are older if the seminoma is the main component.

Morphology

The gross aspect and the micromorphology strongly depend on the amount of the single histologic components (Figures 6.49 and 6.50). The various types are randomly mixed; nevertheless, certain combinations are significantly more frequent than others. Embryonal carcinoma is the most frequent (80%) single component, but teratoma and YST show statistically the strongest correlation (Table 6.17).[124] Seminoma is a component of about 15% of all mixed TGCTs, preferentially combined with embryonal carcinoma.

Figure 6.49
Gross appearance of a 'mixed' germ cell tumor invading the spermatic cord.
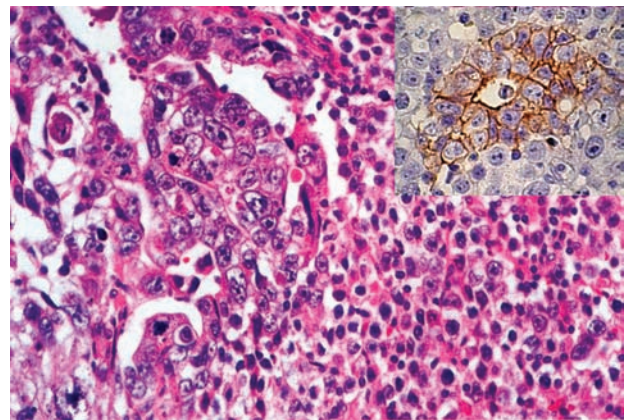
Figure 6.50
Combination of embryonal carcinoma with pseudoglandular structures (left) and seminoma (right).The insert shows the embryonal carcinoma cells immunohistochemical reactive for cytokeratin (CAM 5.2).

Table 6.17 Preferred pairing of different tumor types in mixed germ cell tumors[124]

	p Value
Teratoma + embryonal carcinoma	< 0.001
Teratoma + yolk sac tumor	< 0.001
Teratoma + seminoma	< 0.001
Embryonal carcinoma + seminoma	< 0.001
Teratoma + choriocarcinoma	0.002
Choriocarcinoma + seminoma	0.002
Choriocarcinoma + yolk sac tumor	0.007
Embryonal carcinoma + choriocarcinoma	0.149
Yolk sac tumor + seminoma	0.552

In the past, the combination of teratoma and embryonal carcinoma was called teratocarcinoma, a term which was subsequently used as a synonym for all NSGCTs.

Prognostic factors

Contrary to seminoma in NSGCTs, the invasion of lymph and/or blood vessels (pT2) is the most powerful predictor of relapse or retroperitoneal metastases. Vascular invasion is very frequent in embryonal carcinomas and, in fact, large amounts of it in a mixed germ cell tumor negatively influence the prognosis (Table 6.18). If the orchiectomy specimen consists of 100% embryonal carcinoma, the patient is at high risk for retroperitoneal metastasis. The pathology report should therefore include a rough estimate of the relative amount as a percentage of embryonal carcinoma. Teratoma and/or YST presence in the tumor are markers of a favorable prognosis.[125]

In the absence of embryonal carcinoma the S-phase fraction of the aneuploid cells as determined by flow cytometry has a prognostic importance. Patients with an S-phase fraction below 29% are at low risk, and those above 29% at high risk for retroperitoneal metastases.[126] High proliferative activity is also correlated with p53 protein expression,[127] which is a marker of aggressiveness in other types of cancer.

Tumor spread and morphology of lymph node metastases

With the exception of hematogenous metastasizing choriocarcinoma, all other NSGCTs primarily metastasize to the retroperitoneal lymph nodes (Figure 6.51). The incidence is obviously correlated with the pathologic (pT) or clinical stage. Roughly about one-third

Table 6.18 Prognostic factors in mixed NSGCTs

■ Vascular/lymphatic invasion	unfavorable
■ High amount (%) of EC	unfavorable
■ In absence of EC S-phase fraction > 29%	unfavorable
■ Presence of teratoma	favorable
■ Presence of yolk sac tumor	favorable

of tumors confined to the testis without vascular invasion (pT1) are accompanied by retroperitoneal metastases or will relapse in the first year after surgery. The percentage increases to about 75% if the tumor involves the spermatic cord and/or scrotum.[128,129] The pattern of tumor spread is the same as in seminoma: ipsilateral para-aortic, iliacal, and, rarely, inguinal lymph nodes. With increasing nodal stage, the probability of organ metastases becomes greater. In the presence of a bulky (>5 cm = pN3) retroperitoneal disease, organ metastases can be expected in more than half of the patients.[128] Lung and liver are the main sites of organ involvement, but the frequency varies in the various published series.

Generally the presence of teratoma and, to a lesser extent, also of YST in the orchiectomy specimen predicts teratoma in the metastases. But teratoma absence in the primary does not exclude its presence in the metastases.[130] Persistence of teratoma is also a common finding (44%) in retroperitoneum after chemotherapy.[131] Also in late recurrences after a temporary complete response to chemotherapy teratoma is the most common tumor type (Figures 6.52 and 6.53), followed by YST and non-germ-cell malignancies.[132]

Clinical features

The symptoms of the mixed germ cell tumors are no different from those of other NSGCTs. The serum markers AFP and hCG are elevated in more than 50% of patients.[133] As already mentioned, patients with tumors composed mainly of embryonal carcinoma will probably have retroperitoneal metastases at the time of diagnosis. For the management of stage I NSGCTs, different risk-adapted strategies can be adopted: surveillance and treatment at relapse, retroperitoneal node dissection with or without adjuvant chemotherapy, and finally adjuvant chemotherapy only.[9] Surveillance is obviously indicated in low-risk patients, whose tumors show no or only one unfavorable prognostic feature (Table 6.19). All three therapy variants are very successful with survival rates which are likely to achieve 100%. Experienced centers have significantly better therapy results than smaller hospitals.

For metastatic tumors three courses of BEP (bleomycin, etopside, cisplatin) lead to survival rates of more than 90%. Residual masses after chemotherapy usually contain teratoma areas and require surgery. Teratoma in residual tumor can undergo later malignant changes (somatic malignancies). The salvage therapy after chemotherapy failure can cure only about 30% of men.
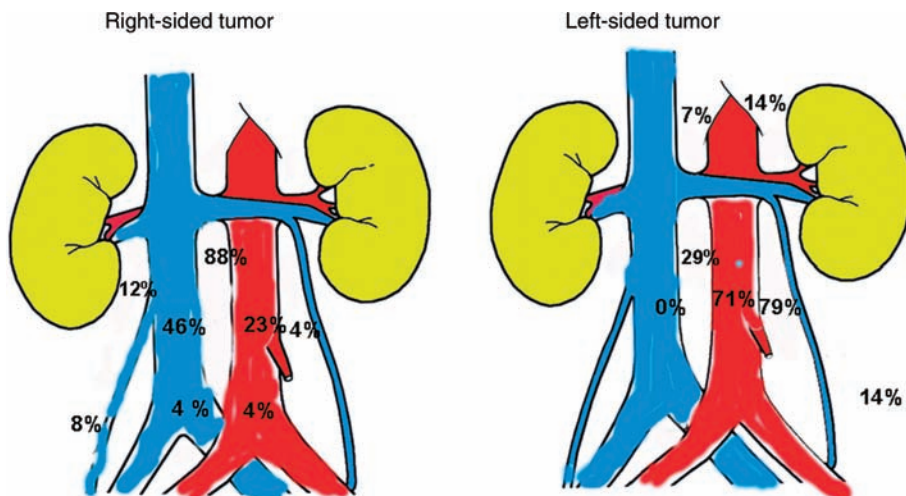
Figure 6.51
Distribution of retroperitoneal lymph node metastases in stage II non-seminomatous germ cell tumors. In the right-sided tumour the intra-aorto-caval and precaval, in the left-sided tumor the pre- and left aortic areas are the preferred location of affected lymph nodes. (Modified after Donohue.[129])
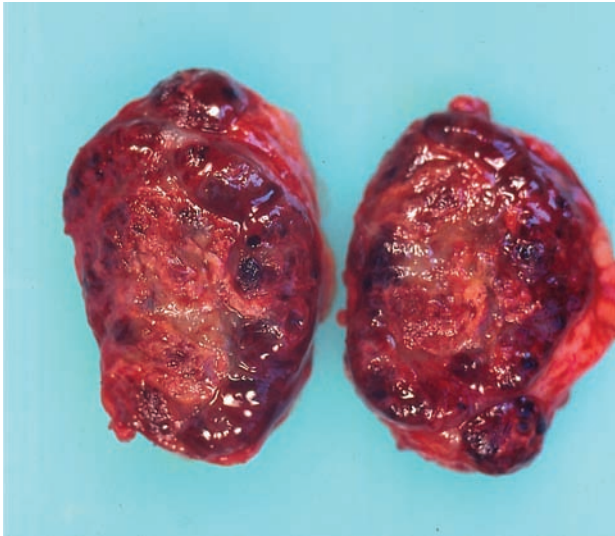
Figure 6.52
Lymph node metastasis of a choriocarcinoma.

Figure 6.53
Lymph node metastasis of a non-seminomatous TGCT after chemotherapy.

are the prevailing primary,[134] in others choriocarcinomas are supposed to be the most frequently regressing tumors.[136] However, the small series published do not allow a thorough statistical analysis.

Clinically, such regressed tumors are palpable only in about 60% of cases. In ultrasonography, suspicious findings such as hyperechogenic lesions and/or microcalcification are present in more than 90% of cases. Primary orchiectomy of the affected gonad is mandatory because the malignancy can persist despite systemic chemotherapy.[137]

Table 6.19 Clinical prognostic classification of metastatic NSGCTs of the International Germ Cell Collaborative Group[9]

Good prognosis 5-year overall survival 91%	TGCT or retroperitoneal GCT No non-pulmonary visceral metastases and AFP < 1000 IU/l HCG < 5000 IU/l LDH < 1.5 × normal
Intermediate prognosis 5-year overall survival 71%	TGCT or retroperitoneal GCT No non-pulmonary visceral metastases AFP < 1000–10 000 IU/l hCG < 5000–50 000 IU/l or LDH < 1.5–10 × normal
Poor prognosis 5-year overall survival 48%	Mediastinal primary or non-pulmonary visceral metastases or AFP > 10 000 IU/l HCG > 50 000 IU/l or LDH > 10 × normal

Burned out TGCTs

So-called extragonadal germ tumors arising isolated in mediastinum and pineal regions are, with few exceptions, true primaries. Primary retroperitoneal germ cell tumors, however, are 'a non-existing entity'[134] and should be considered metastases of a small occult viable or completely regressed ('burned out') germ cell tumor located in the testis. In an autopsy series of metastasizing TGCTs, burned out tumors represented approximately 10% of all cases.[135]

The testes involved can appear normal or show a circumscribed scar (Figure 6.54), which is also the most common histologic finding.[134] Normal appearing or fibrotic organs show foci of atrophic or collapsed seminiferous tubules, which frequently (49%) contain atypical germ cells (IGCNUs).[47,134,135]

Which kind of TGCT shows the highest proportion of regressed primary neoplasms is not really known. In some reports seminomas

Figure 6.54
A burned out (scar) germ cell tumor in the testis of a patient with a so-called primary extragonadal (retroperitoneal) seminoma.

Staging

The TNM staging system (Table 6.20) is generally accepted now as the system which can be used in the clinical and pathologic (pT = postsurgical; yT = after chemo- or radiotherapy) assessment of the local tumor, nodal involvement, and eventual organ metastases. With the introduction of the S group the information on the serum marker status is included in the algorithm. The only criticism is that the prognostic criteria for seminoma and NSGCTs are completely different. Tumor diameter and invasion of rete testis are important in seminoma but not in NSGCTs, whereas the vascular invasion (pT2) is extremely important in NSGCTs but not so much in seminoma.

Clinical staging systems (Table 6.21) are based more on the presence, size, and location of metastases and completely disregard the extent of the primary tumor and all other prognostic important factors. They are 'homemade' for specialized institutions and are generally very useful for therapy planning, but too superficial for epidemiologic studies.[138]

Intra-operative frozen section diagnostic of TGCTs

In the past, intra-operative frozen section diagnosis has been strictly rejected by pathologists because of diagnostic uncertainty.[139] Occasionally, however, testis sparing surgery because of lonely testis, bilateral tumors, or suspected non-germ cell tumor requires an intra-operative assessment. The diagnostic results are good in mature teratomas, dermoid cysts, and non-germ-cell tumors. The assessment of resection margins in partial tumor resections is not difficult, but for the detection of IGCNU the method is useless and should not be applied.

Table 6.20 pTNM (AJCC/UICC) staging of TGCTs

pTx	Unknown status of testis
pT0	No apparent primary (includes scars)
pTis	Intratubular tumor, no invasion
pT1	Testis and epididymis only; no vascular invasion or penetration of tunica albuginea
pT2	Testis and epididymis with vascular invasion or trough tunica albuginea to involve tunica vaginalis
pT3	Spermatic cord
pT4	Scrotum
pNx	Unknown nodal status
pN0	No regional node involvement
pN1	Node mass or single nodes ≤ 2 cm; ≤ 5 nodes involved (no node ≤ 2 cm)
pN2	Node mass > 2 cm but < 5 cm; or > 5 nodes involved
pN3	Node mass > 5 cm
pMx	Unknown status of distant metastases
pM0	No distant metastases
pM1a	Non-regional nodal or lung metastases
p1Mb	Distant metastases other than non-regional nodal or lung metastases
SX	No marker studies available
S0	All marker levels normal

	LDH	hCG (mIU/ml)	AFP (ng/ml)
S1	<1.5 × N	+ <5000	+ < 1000
S2	1.5–10 × N or	5000–50 000 or	1000–10 000
S3	> 10 × N or	> 50 000 or	> 10 000

N = normal value.

Table 6.21 Different clinical staging

AJCC/UICC system

Stage 0	Tis, N0, M0, S0
Stage IA	T1, N0, M0, S0
Stage IB	T2-T4, N0, M0, S0
Stage IC	any T, N0, M0, S1–S3
Stage IIA	any T, N1, M0, S0–S1
Stage IIB	any T, N2, M0, S0–S1
Stage IIC	any T, N2, M0, S0–S1
Stage IIIA	any T, any N, M1a, S0–S1
Stage IIIB	any T, any N, M0–M1a, S2
Stage IIIC	any T, any N, M0–M1a, S3 or any T, any N, M1b, any S

Royal Marsden

I	testis only
IM	continued positive serologic evidence of tumor after orchiectomy
II	infradiaphragmatic nodal involvement
IIA	< 2 cm
IIB	2–5 cm
IIC	> 5 cm
III	supraclavicular or mediastinal involvement
IV	extranodal metastases
IVL	Lung metastases
IVH	Liver metastases

Memorial Sloan Kettering Cancer Center

A	testis and adnexa
B	infradiaphragmatic nodal metastases
B1	< 5 cm
B2	5–10 cm
B3	>10 cm
C	spread beyond retroperitoneal nodes

Massachusetts General Hospital

I	testis only
II	retroperitoneal involvement
IIA	< 2 cm
IIB	≥ 2 cm
III	supraclavicular and mediastinal involvement
IV	disseminated disease

MD Anderson

I	testis only
IIA	negative lymphangiogram but pathologic positive retroperitoneal nodes
IIB	positive lymphangiogram
IIIA	supraclavicular nodes
IIIB1	gynecomastia lacking gross tumor
IIIB2	lung metastasis (no more than 5 nodules per lung and not >2 cm)
IIIB3	advanced lung
IIIB4	advanced abdominal or obstructive uropathy
IIIB5	visceral disease, excluding lung

Part 5

Tumors of sex cord/gonadal stroma

These are very rare tumors which, in large series, account for 1.6–6%[1,2,138] of adult testicular tumors and are somewhat more frequent in children (Table 6.22). Absolutely nothing is known about the epidemiology, histogenesis, and possible etiology of these tumors which derive from Leydig, Sertoli, granulosa, and theca cells. They arise in the testis as well as in the ovary but the incidence of the single histologic types is quite different in the two genders. Leydig and Sertoli cell tumors are more frequent in the male gonads; granulosa and theca cell tumors are typical for the ovaries and rare in the testes. Teilum[140] defined the term gonadal stroma tumor as a histogenetic and morphologic name for tumors of both genders, which derive from an undifferentiated gonadal mesenchyme. These tumors reflect the different development phases of the male gonad in their morphology. The name *androblastoma* has been used in the past synonymously for all gonadal stroma tumors or for Sertoli cell tumors alone, which has been rather confusing.

In the WHO 2004 (Table 6.1) classification pure forms with one cell type, mixed forms composed of two cell types, and incompletely differentiated tumors are listed. In contrast to old classifications, this category also includes very peculiar tumors containing both germ cells and sex cord/gonadal stromal elements.

Leydig cell tumors (benign and malignant)

Interstitial cell tumor

Epidemiology

Leydig cell tumors (LCTs), at 1–3% of all testicular neoplasms, are the most frequent type in this category and represent 4–9% of all primary testis tumors in prepubertal males. The age of the patients ranges from 2 to 90 years.[141] The average age (46 years) is clearly higher than that of TGCTs. In 5–10% of cases an association with cryptorchidism[141] has been determined, but it is unknown whether this is pure coincidence or if there is a true causal relationship. About 3% of tumors are bilateral.

Morphology of benign forms

LCTs are usually well-circumscribed, yellow-brownish tumors with a thin capsule (Figure 6.55). They can be lobulated by fibrous septa and show foci of necrosis or small hemorrhages (25%). The average diameter in the large series was 3 cm[141] and extension to the rete testis or spermatic cord was observed in more than 10–15% of cases.[141]

The tumor cells are large and polygonal with abundant eosinophilic cytoplasm (Figure 6.56), which occasionally can be

Figure 6.55
Macroscopic appearance of a Leydig cell tumor.
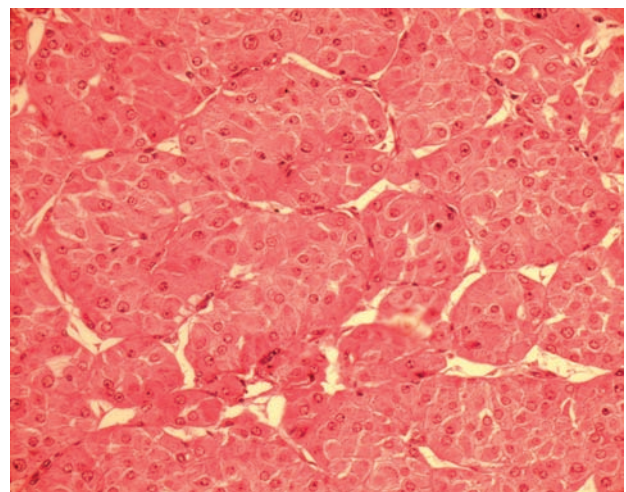
Figure 6.56
Benign Leydig cell tumor. The morphology of the tumor cells is identical with that of the normal counterpart.

Table 6.22 Frequency and typical age of the patients with sex cord/gonadal stroma tumors

	Testis tumors (%)	Average age (years)	Range
Leydig cell tumor	1–3	46	2–90 years
Sertoli cell tumor	0.4–1%	45	1½–80 years
Granulosa cell tumor			
adult type	≈ 24 cases		42 years
juvenile type	Most common tumor in children	≤ 6 months	0–7 months

Table 6.23 Immunoreactivity (%) of different sex cord/gonadal stroma tumors with the routinely used antibodies[68,143,144]

	Inhibin	CK	S-100	Sm-Actin	Calretinin	CD99	Vimentin	Melan A
Leydig cell tumor	96	44	27		92	50	92	100
Sertoli cell tumor	40	80	30	56	33	30	83	
Granulosa cell tumor	98	44	42	90	100	79	100	

granulated or vacuolated because of intracytoplasmic fat accumulation. LCTs with spindle cell differentiation are rare.[142] In one-third of cases, the cytoplasm contains Reinke crystals and, in 15%, lipochrome pigment.[143] The nuclei are usually perfectly round and contain a big nucleolus. In a few cases, a marked variation of size and shape occurs. The mitotic activity is, with some exceptions, generally low. Tumor cells arranged in a solid formation with scanty fibrous stroma is the most common growth pattern. However, trabecular or pseudotubular structures with prominent stroma and even psammoma-like calcification have been observed in single cases.

LCTs can generally be easily recognized, but in some less well-differentiated cases confusion with lymphomas or plasmacytomas is possible. The use of immunohistochemistry can help to avoid mistakes (Table 6.23). Leydig cells react with a large number of antibodies but the reactions with α-inhibin and melan-A are almost always positive.[142,144,145]

Another similar lesion is the *malakoplakia* (granulomatous orchitis) of the testis, which is an exuberant histiocytic reaction to infection, probably with *E. coli*.[146] The macrophages have a large eosinophilic cytoplasm which contains target-like inclusions called Michelis Gutmann bodies (Figure 6.57).

A marked Leydig cell hyperplasia in atrophic testis of the Klinefelter syndrome can also easily be confused with LCTs if the pathologist does not know the clinical history (Figure 6.58). However, a few true LCTs have been described in a Klinefelter testis.[147] In untreated *adrenogenital syndrome* masses of 'steroid cells' similar to the Leydig cells develop in the interstitium of both testes.[148,149] The masses disappear after corticosteroid therapy, making surgery unnecessary.

Morphology of malignant forms

The most reliable criterion of malignancy is the size of the tumor – the diameter of malignant LCTs is usually greater than 5 cm (average 4.7 cm versus 2.6 cm for benign tumors).[150] There is no significant difference in the cytomorphology between benign and malignant Leydig cells, but atypical mitotic figures are more frequent and the mitotic index is significantly higher in malignant tumors (mean 13.9 vs 1.9).[150] Also, the activity of the proliferation marker MIB-1 is higher in malignant tumors (mean 18.6% vs 1.2%). Vascular invasion (Figure 6.59), infiltrative margins, and necrosis are also associated with malignancy, but used as a single criterion are not very reliable (Table 6.24). Mostly malignant LCTs show a combination of more than four of such malignancy predicting features.[141]

Metastatic LCTs commonly first involve the retroperitoneal lymph node (72%). Blood-borne metastases are located in the lung (43%), the liver (38%), and the bones (28%),[151] but in single case reports other sites have also been described.
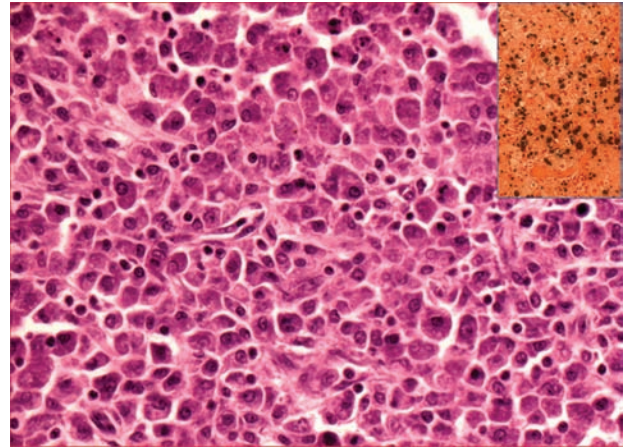
Figure 6.57
Large macrophages in a malakoplakia of the testis. The insert shows intracellular calcifications (black) – the Michelis Gutmann bodies.
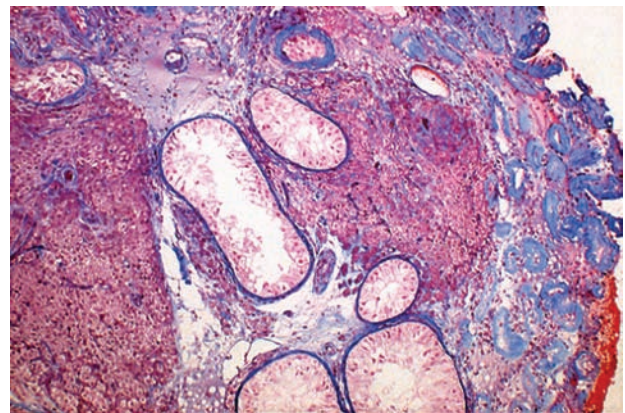
Figure 6.58
Klinefelter syndrome with nodular hyperplasia of the Leydig cells mimicking small tumors. The seminiferous tubules are atrophic.

Cytogenetics

All metastasizing LCTs but also more than one-third of benign ones are DNA aneuploid. The only constantly encountered aberration is the gain of the X chromosome, on which a lot of genes involved in
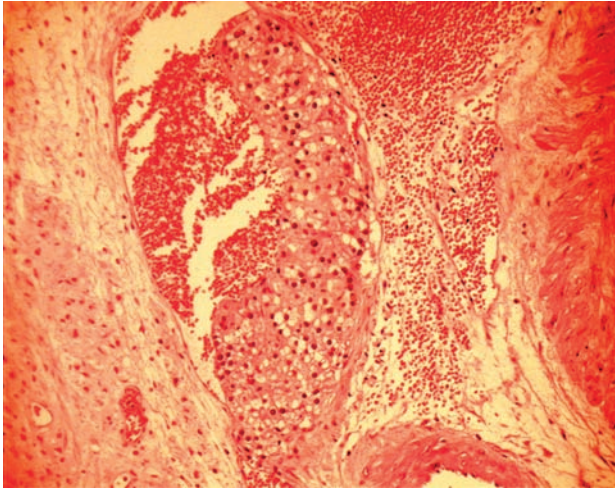
Figure 6.59
Leydig cell tumor with vascular invasion of the tumor cells – a morphologic feature suggesting malignancy.

Table 6.24 Ranking of malignancy criteria in Leydig and Sertoli cell tumors

Leydig cell tumor	Sertoli cell tumor
Adults (never in infants)	Any age Gynecomastia > 30%
	Diameter > 5 cm High mitotic activity* Vascular invasion* Infiltrative margins* Necrosis*

* Not very reliable, used as a single criterion – minimum of 2 criteria needed.

the development of the testis, infertility, and the gene coding for the androgen receptor are located.[152]

Clinical features

LCT of the testis usually presents as an ultrasonographically hypoechoic testicular mass, accompanied by endocrine symptoms in 20% of the cases. In adults, feminization with gynecomastia, loss of libido, and impotence are the symptoms caused by a decreased testosterone/estradiol ratio and a high hydroxyprogesterone/androstenedione ratio.[153] After orchidectomy gynecomastia does not regress in all cases[154] and spermatogenesis can remain impaired, because the excess of female hormones leads to an irreversible atrophy and sclerosis of the seminiferous tubules. The feedback mechanisms with the pituitary (hypophysis–gonadal axis) and subsequently also the androgen production in the testis normalize in a few months.[154]

In contrast to adults, LCTs in infancy produce androgens and cause a precocious pseudopuberty, which is characterized by pubertal enlargement (growth) of the genital organs without induction of spermatogenesis.

Intra-operative frozen sections are very useful in the diagnosis of small sex cord stromal tumors which can be treated with local excision.[139] Although in frozen section some diagnostic problems exist, the correlation with the final diagnosis made on paraffin-embedded material is excellent.[155,156]

In adults approximately 10% of LTCs are malignant; in children the tumor is always benign. Clinically, malignancy is established by the presence of metastasis at the time of diagnosis or during follow-up. There is currently no effective treatment for the metastasis. Some clinicians advocate a retroperitoneal lymph node dissection immediately after orchidectomy, especially in patients with small tumors.[157] Due to the small number of cases the therapeutic results are obviously unknown. Short-lived response to chemotherapy and a questionable benefit of radiotherapy document the therapeutic dilemma. The median survival rate for all stromal tumors (Sertoli inclusive) is 1.2 years. In single cases metastases have been observed even many disease-free years after LCT resection.[158]

Sertoli cell tumors (benign and malignant)

Epidemiology

Sertoli cell tumors (SCTs) occur significantly less frequently than LTCs and account for 1% of all testicular tumors.[159] At an average age of 45, the patients are as old as those with LTCs; but these tumors are extremely rare in men younger than 20. Many cases published in the past were probably the similar-in-appearance juvenile granulosa cell tumors. Single cases are associated with the androgen insensitivity syndrome,[148] Peutz–Jeghers syndrome,[160] and the Carney syndrome.[161] Malignant SCTs are rare but occur at any age, even in children. Ten percent of SCTs are malignant.[162,163]

Morphology of benign form

The tumors are usually well circumscribed with a sclerotic border and a tan-gray, white, or yellow color (Figure 6.60). Necrotic areas are rare but hemorrhagic spots can be seen in one-third of cases.[159] The sizes reported range from 0.3 to 15 cm, but the average diameter is 3.6 cm. The micromorphology varies from well-differentiated, easily recognizable Sertoli cells to less-differentiated forms which are recognized primarily through their typical arrangement in hollow or solid tubules (Figures 6.61 and 6.62). The cells can also grow in solid cords, trabeculae, or small nodules surrounded by a fibrous or hyaline stroma. Usually the cytoplasm is eosinophilic, but sometimes it contains large amount of lipids – the *lipid-rich variant* (Figure 6.63), which is listed in the WHO 2004 classification, though not as a distinct entity.

In some few reported cases the exuberant sclerotic stroma has been the morphologic hallmark. Since these tumors are also smaller and occur only in adults, they were classified as a distinct variant called *sclerosing Sertoli cell tumor* (Figure 6.64).[2,164]

SCTs have to be differentiated from *Sertoli cell nodules* (hypoplastic zones; Sertoli cell congeries) frequently present in cryptorchid but also normal testes. The nodules consist of small aggregates of seminiferous tubules with a prominent, thick basement membrane and lined solely by Sertoli cells.[165]

Figure 6.60
Gross appearance of a well-circumscribed Sertoli cell tumor.

Figure 6.61
Well-differentiated Sertoli cell tumor with tubular structures resembling seminiferous tubules.
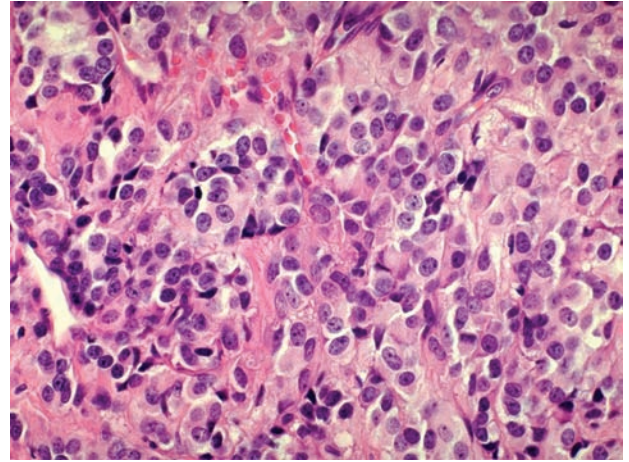
Figure 6.62
A less well-differentiated clinically malignant Sertoli cell tumor.
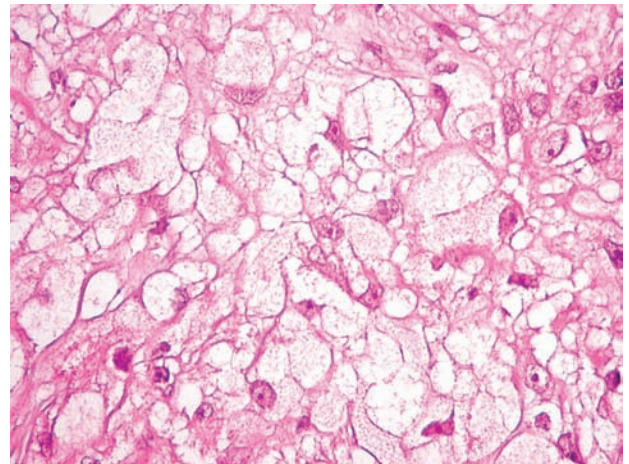
Figure 6.63
Tumor cells with lipids in cytoplasm – the so-called lipid rich variant of Sertoi cell tumor.

Figure 6.64
Sclerosing Sertoli cell tumor is a rare variant of this tumor type.

Also *adenomatoid tumors*, extremely rare in the testis, can be mistaken for SCTs. The cells of adenomatoid tumors react positively immunohistochemically with cytokeratin and vimentin antibodies, which Sertoli cells do as well (Table 6.23). However, SCTs also react with inhibin (50%), CD99, and S-100 protein (30%), which adenomatoid tumors do not (Figure 6.65).
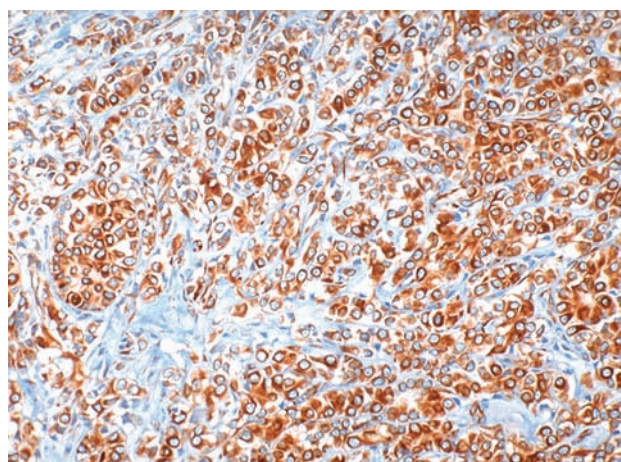
Figure 6.65
Sertoli cell tumor: immunohistochemical reaction with α-inhibin antibodies.

It would be a tragic mix-up to mistake the malignant tubular type of seminoma for a benign Sertoli cell tumor, whose cells are always negative for PlAP, a specific marker of germ cells.

Morphology of malignant forms

Malignant SCTs differ from their benign counterpart mainly in size: their diameter is on average >5 cm. Necrosis and hemorrhage are also more frequent. Microscopically the cells show a marked nuclear atypia and per high power field (objective 40×) the number of mitoses is usually greater then 5 (Figure 6.62). Lymphovascular invasion is common but not seen in all malignant cases.[159,166]

Cytogenetics

In the only analysis performed so far of eight cases, a gain of chromosome X followed by loss of the entire or part of chromosome 2 was detected.[168]

Clinical features

The cardinal symptom is a mass described as 'slowly enlarging' (average 3.7 years!), causing pain in a minority of cases.[159] The only hormonal manifestation is gynecomastia present in one-third of malignant SCTs,[2] and in benign tumors, although not as frequent as generally assumed (25% of cases).[159] Feminizing symptoms[169] were observed in SCTs combined with Peutz–Jeghers syndrome, which is an autosomal dominant disorder characterized by the association of mucocutaneous pigmentation and multiple gastrointestinal hamartomatous polyps and increased tumor risk.

Malignant SCTs metastasize to the retroperitoneal, inguinal, and supraclavicular lymph nodes as well to the lung and bones.[162] No specific therapy exists. Retroperitoneal lymph node dissection is performed in cases in which the morphology is suggestive of malignancy,[170] but the benefits of this procedure are still unproven.

Large cell calcifying Sertoli cell tumor (benign and malignant)

Epidemiology

So far about 60 cases of this new nosologic entity, first described in 1980,[171] have been reported. Large cell calcifying Sertoli cell tumor (LCCST) can occur in phenotypically normal men or associated with hormonal or genetic disorders like Peutz–Jeghers and Carney syndromes[161] (Table 6.25). The tumor can arise at any age but patients with benign LCCST are 17 years old on average (range 2–38 years), that is, younger than those with the malignant counterpart who are on average 39 years old (range 28–74 years).[172,173] Benign tumors are multifocal and bilateral in 28% of cases, malignant ones solitary and unilateral.[172]

Interestingly, LCCST is the only gonadal stroma tumor which has never been described in the ovaries.

Morphology

Benign tumors are confined to the testis; malignant ones can extend to the neighboring organs. Benign LCCSTs are small (0.8–2.3 cm) whereas malignant ones have an average diameter of 5.4 cm (range 2–15 cm) and can replace the entire testicular parenchyma. Foci of necrosis and hemorrhage are typical for the malignant LCCSTs. The color varies from tan-white to yellow or gray; grossly apparent calcifications are identified in benign as well as malignant tumors.

Large, irregularly shaped and confluent calcification, and even ossification, is the microscopic hallmark (Figure 6.58), regardless of the tumor's biologic behavior (Figure 6.66). A typical tumor cell has abundant eosinophilic cytoplasm and round nuclei (Figure 6.67), more closely resembling the Leydig than the Sertoli cell – in fact, the true histogenetic origin has been revealed by electron microscope analysis.[174] The cells are arranged in solid nests or cords embedded in a myxomatous stroma. Malign LCCSTs do not have a different morphology with the exception of a brisk mitotic activity (4–14 mitoses/10 hpf). Even vascular invasion is not encountered in all cases. Thus, metastases are the only objective evidence of malignancy. The extensive calcifications are so characteristic that LSCCT can hardly ever be mistaken for another testicular tumor.

Table 6.25 Large cell calcifying Sertoli cell tumor and associated syndromes

Age (years)	Benign	average 17	(range 2–38)
	Malignant	average 39	(range 28–73)
Location	Benign	28% bilateral and multifocal	
	Malignant	unilateral and unifocal	
In young patients in association with			
Carney syndrome			
Peutz–Jeghers syndrome			
Gynecomastia			
Tuberous sclerosis			
Androgen insensitivity syndrome			
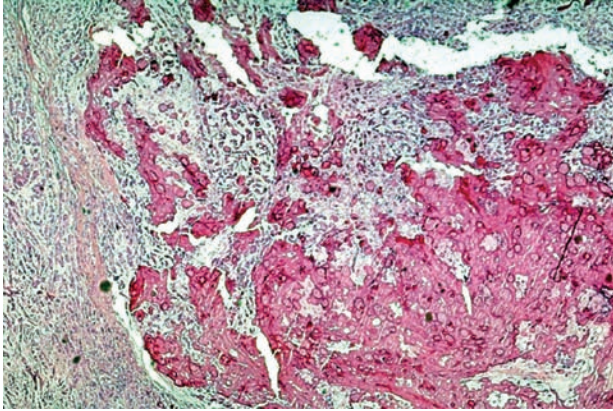
Figure 6.66
Large irregularly shaped calcification typical for large cell calcifying Sertoli cell tumor.

Granulosa cell tumor of adult type

Granulosa cell tumor of adult type is probably the rarest tumor arising in the testis, with only 21 cases reported to date.[175] The youngest patient was 16, the oldest 60 years old. The morphology does not differ from those arising in the ovary. The tumor diameters range from 0.7 to 13 cm; the color is yellow. The cut surface is lobulated and small cysts can be present. Histologically the patterns are diffuse (Figure 6.60) or microfollicular, with typical Call Exner bodies. The cells have scanty cytoplasm and the nuclei are all grooved like coffee beans (Figures 6.68 and 6.69).

Slow enlargement of the testis and, in 20%, gynecomastia are important symptoms. Serum inhibin and anti-mullerian hormone (AMH) can be elevated. In four cases (20%) intra-abdominal metastases have been described. Morphologic criteria of malignancy are unknown.

Figure 6.67
The cells of the large cell calcifying Sertoli cell tumor more closely resemble the Leydig than the Sertoli cell.
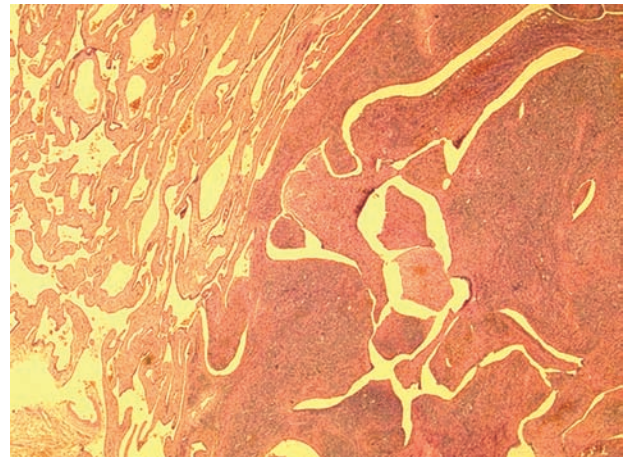
Figure 6.68
Overview of an adult type granulosa cell tumor with small cystic spaces.

Clinical features

A testicular mass causing discomfort is the leading symptom in all cases. In young patients, association with different genetic disorders like Peutz–Jeghers syndrome, androgen insensitivity syndrome, tuberous sclerosis, and gynecomastia is rather frequent. LCCST can be a part of Carney syndrome,[161] whose other characteristics are skin pigmentation, endocrine overactivity (Cushing syndrome, acromegaly), and multiple myxomas localized in the breast, skin, and heart. Young patients with LSCCT, as well as their relatives, consequently have to undergo cardiologic examination due to association with cardiac myxoma, which can cause a sudden death.

Malignant LCCSTs do not manifest associations with genetic disorders. They spread to the retroperitoneal lymph nodes and also via the bloodstream to bones, liver, and lungs. Retroperitoneal lymph node dissection is a standard therapeutic procedure in the initial stages. Radiation and chemotherapy have been used in non-resectable cases with some benefit, but a specific therapy does not yet exist.[172]

Figure 6.69
The typical cytomorphology of the granulosa cell tumors with the grooved, coffee bean like nuclei.

Granulosa cell tumor of juvenile type

The juvenile type is the most common testicular tumor in the first 6 months of life and accounts for 6% of all prepubertal testicular tumors.[176,177] The cut surface of the tumor is microcystic. Microscopically, the cysts are lined by cells resembling granulosa cells (Figure 6.70). Among the cysts, tubules with proliferated Sertoli cells form bizarre structures (Figure 6.71). The high mitotic count can erroneously suggest malignancy. Because of the age of the patients and, to a lesser degree, because of similarities, the tumor is confused with the yolk sac tumor; this can be a tragic mistake, since the juvenile granulosa tumor is absolutely benign and does not require any therapy other than simple surgical enucleation.[177]

In 30% of cases, the tumor is located in an intraabdominal cryptorchid testis and 20% of children have ambiguous genital organs. In such cases numerical aberrations of the XY chromosomes (mosaic 45X/46XY) or structural anomalies of Y chromosome[176,177] were described.

Thecoma – fibroma type tumors

The 25 known cases[2,179] were observed in men in their fourth to fifth decade. The tumors are firm, white, and well circumscribed. The spindle cells resemble fibroblasts with respect to the structure of the ovary's cortical area. Malignant cases are unknown.

Mixed forms and incompletely differentiated gonadal stroma tumors

Mixed tumors usually contain well-differentiated Leydig cells and less-differentiated Sertoli cells (Figure 6.72), but combinations with granulosa cells also occur. The incompletely differentiated cells consist of spindle or more epitheloid cells and can contain some differentiated elements (Figure 6.73). Single cells can react with inhibin, but usually they are positive only for smooth muscle actin and S-100 protein.[180,181] The classical cytopathologic hallmark of malignancy can be missed even in metastasizing cases, but large size is an important predictor.

Patient age ranges from 6 months to 60 years.[59] Few cases have presented with gynecomastia. In childhood the tumors are perfectly benign, whereas one-qutarter of tumors in adults metastasized to the retroperitoneal lymph nodes and/or abdominal organs.

Figure 6.70
Juvenile granulosa cell tumor with follicle-like cysts lined by cells resembling granulosa cells.
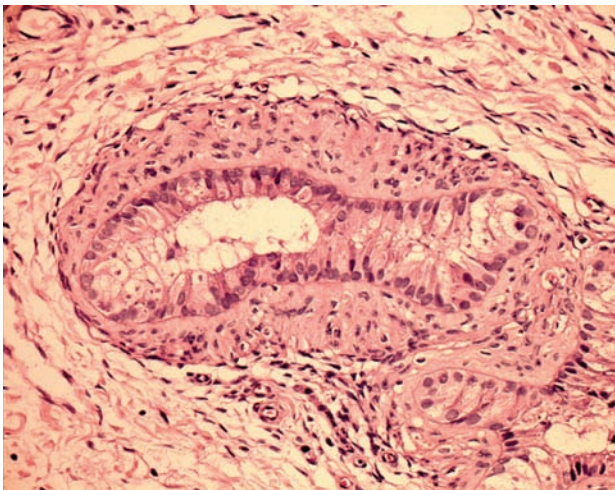
Figure 6.71
Juvenile granulosa cell tumor: tubules with proliferated Sertoli cells form bizarre structures.
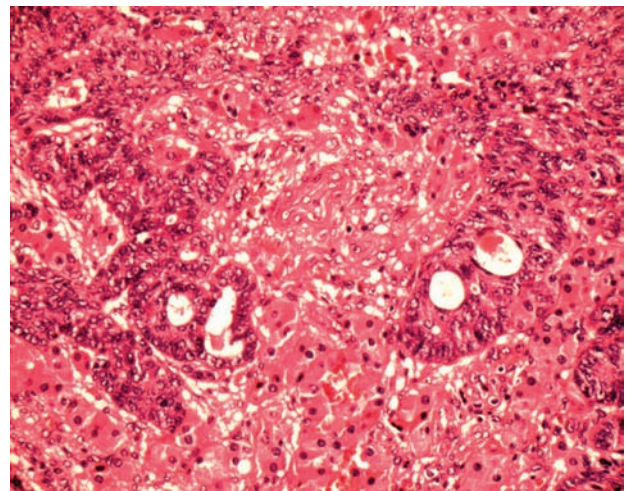
Figure 6.72
Mixed gonadal stroma tumor containing well-differentiated Leydig cells and less differentiated Sertoli cells.
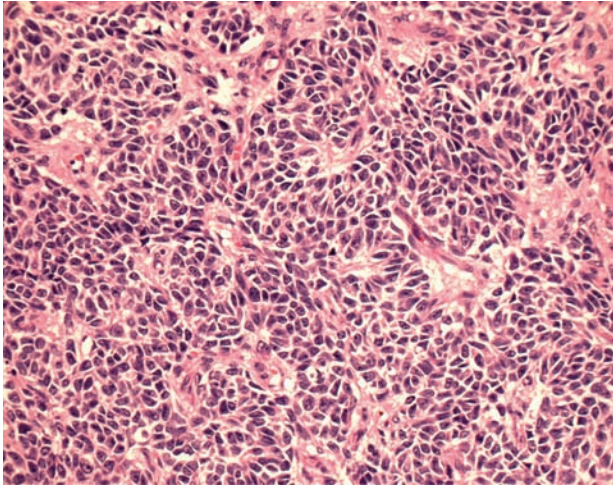
Figure 6.73
Incompletely differentiated gonadal stroma tumors consist of spindled or more epitheloid cells.

Figure 6.74
Overview of gonadoblastoma: the large seminoma cells are surrounded by small indifferent stromal cells. Hyalinization and conspicuous calcification are the hallmarks of this tumor.

Mixed germ cell/sex cord/ stromal tumor

Two types of tumors which are composed of a mixture of germ and gonadal stroma cells can arise in the testis. The most common is gonadoblastoma, which was described by Scully in 1953[182] and affects only dysgenetic gonads. The other one, first observed in the ovary,[183] used to be simply called 'mixed germ cell sex cord–stromal tumor' and is not related to intersexuality. This tumor has been questioned by some authors,[184] who considered the germ cells to be entrapped in a stromal tumor and not a genuine part of it. But new studies of further cases[185] dissipated all doubts about the existence of this rare entity, which actually was first described in 1912 by the famous French pathologist Masson (Paris/Montreal) under the name 'Pflügeroma'.[186]

Gonadoblastoma

Epidemiology

Gonadoblastoma arises more commonly in individuals who are phenotypically female (80%) than in those who are phenotypically men.[187] In a series of 98 testicular tumors affecting children younger than 12, gonadoblastoma was diagnosed in two cases (2%).[188] More than 90% of these tumors are diagnosed in the first three decades of life. Affliction of both gonads is common (30–40%).

Morphology

The tumors have a yellow cut surface and in one-quarter of cases can be detected only microscopically. On the other hand, large tumors (Ø =8 cm) replacing the entire testicular parenchyma are also not uncommon. The histology is unique with small nests of seminoma and, alternatively (Figure 6.74), but more rarely, embryonal carcinoma cells, which are wreath-like, surrounded by Sertoli and granulosa cells. Leydig cells may also be present. Immunohistochemically
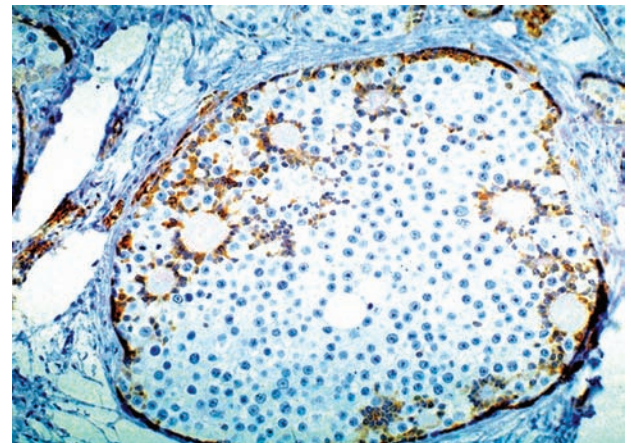
Figure 6.75
Gonadoblastoma: inhibin stained Sertoli cells (brown) surrounding typical seminoma cells with clear cytoplasm.

staining the germ cells with PlAP or vice versa of the stromal cells with inhibin confers on these formations a richly contrasting appearance (Figure 6.75). The center of the nests can contain hyaline nodules, which can calcify and give the tumor a gritty consistency.

In case the tumor is not removed in time, the germ cell component will overgrow the stromal cells and an overt seminoma or, rarely (8%), a NSGCT will develop.

Cytogenetics

Gonadoblastoma arises only in intersex patients with a Y chromosome. The candidate gene *TSPY* (testis-specific-protein-Y) is located in the pericentromeric region of the short arm (Yp11.1-Yp11.2). TSPY protein is normally expressed in spermatogonia but also IGCNU, seminoma, and prostate cancer.[189] TSPY protein can be detected in gonadoblastoma immunohistochemically.

Clinical features

The highest risk for gonadoblastoma is in patients with gonadal dysgenesis (46XY,46X/46XY) with intra-abdominal dysgenetic testes and/or streaks.[189] Also belonging to the same high-risk group are patients with partial androgen insensitivity syndrome with non-scrotal testes and those with Fraiser and Denys–Drash syndrome.[190,191] Both syndromes are characterized by gonadal dysgenesis and glomerular diseases of the kidney, because of different mutations of WT1 (Wilms tumor) suppressor gene, which is involved in the development of the gonads. Patients with Turner syndrome (Y+) and complete androgen insensitivity syndrome have a lower or intermediate degree of risk. In high-risk patients prophylactic gonadectomy is required. Surveillance or irradiation can be adopted for the patient with a minor degree of risk.

In case the neoplastic germ cells (seminoma, embryonal carcinoma) have already overgrown the gonadal stroma components, therapy follows the standard protocols for germ cell tumors.

Germ cell sex cord/gonadal stromal tumor, unclassified

This is the official WHO name for mixed germ cell and gonadal stromal tumors which arise in geno- and phenol-typical normal adult male individuals. Since only a few cases have been reported to date,[185] our knowledge is limited. The reported tumors presented as slow growing testicular masses with a diameter up to 7 cm. The tumors are well-circumscribed white masses, which can totally replace the testicular parenchyma.

The tumors consist of germ cells with clear cytoplasm, which are dissimilar from those of seminomas or embryonal carcinomas. These cells are arranged in small clusters surrounded by the predominant stromal component with inhibin-positive small, indifferent, often spindled cells. Germ cells do not react with the classical markers PlAP and c-kit.

The simultaneous occurrence of a germ cell tumor and a stromal tumor in the unilateral testis is an extremely rare event and is a pure coincidence without any common genetic or oncogenetic background.

Part 6

Miscellaneous tumors of the testis

This major subgroup of the WHO 2004 classification[2] includes various tumors of mostly unknown histogenesis.

Carcinoid

Carcinoids arising in teratoma are classified as 'teratomas with somatic type malignancies'. In case remnants of a germ cell tumor cannot be detected, it should be diagnosed as a distinct entity. Moreover, gut carcinoids can metastasize to the testis.

Epidemiology

From the 80 well documented cases of testicular carcinoid observed, 19 (24%) were associated with teratoma.[192] They account for 0.2–1% of all tumors of the testis in the various statistics. Patients' ages ranged from 19 to 83 years.

Morphology

The tumors measure 0.5–14 cm and the color is yellow to tan and the cut surface solid. The typical carcinoid cells are arranged in a so-called insular growth pattern, which means islets of tumor cells are surrounded by thin fibrous septa (Figure 6.76). Tumor cells are immunoreactive for the classical neuroendocrine markers (NSE - neuron-specific enolase, chromogranin A, synaptophysin) as well as for the specific peptide hormones produced by carcinoids (gastrin, serotonin, etc.).

Clinical features

At the initial examination, patients present with a testicular mass with or without associated pain. A small number (11%) suffer from carcinoid syndrome caused by hyperserotonemia ('flush syndrome'). Prognosis after surgery is excellent except in the rare cases (13%) with metastases, which have a poor outcome.

To rule out the possibility of metastasis resulting from an extratesticular primary carcinoid, thorough postoperative whole-body surveys with imaging devices are essential.

Tumors of ovarian (Müllerian) epithelial types

The entire spectrum of ovarian epithelial tumors has also been described in the testis (Table 6.1). They can originate from the appendix testis, which is a Müllerian rest, or from a so-called Müllerian
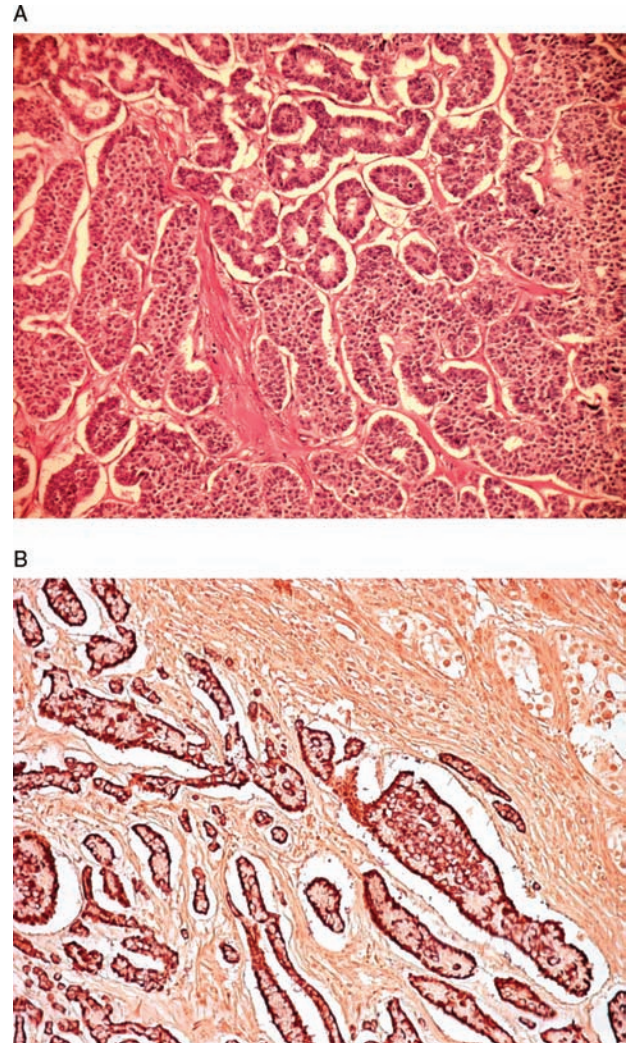
Figure 6.76
(A) Testicular carcinoid with the typical 'insular' growth pattern.
(B) Grimelius stain of intratesticular carcinoid.

metaplasia of the tunica vaginalis testis.[193] They are obviously rare; the most frequent with about 40 reported cases, are the serous tumors, followed by the mucinous with 15 reports.[194–196] The majority of the reported tumors were located somewhere in the epididymotesticular groove.[197] In the past, such tumors have been reported as 'adenocarcinoma of the appendix testis' and sometimes were even confused with mesotheliomas of the testicular tunics.

Epidemiology

Ovarian epithelial type tumors of the testis arise in adults with an average age of 55, in the ranges of 14–77 years for the serous and 11–69 years for the mucinous types.

Morphology

Benign and borderline tumors are cystic; carcinomas tend to be firm. Depending on the lining epithelium, the cysts contain either a serous fluid or a gelatinous material. In serous tumors the epithelia form small papillae protruding in the lumen (Figure 6.77).

Serous cystadenomas and cystadenocarcinomas are lined by a columnar, frequently ciliated epithelium which is bland in benign tumors and more atypical with a variable amount of mitotic figures in borderline lesions (Figure 6.78). Papillae and psammoma bodies are typical for serous differentiation. Invasion of the capsule could be a sign of malignancy, as in the ovarian counterpart.

Mucinous cystadenomas are lined by columnar cells with basally situated nuclei. *Borderline tumors* and mucinous *cystadenocarcinomas* are lined by intestinal-type cells, which produce large amounts of mucin (Figure 6.79). Extravasated mucin and dystrophic calcifications are further hallmarks of borderline or malignant cases.

Other tumors reported in the literature were: one endometrioid carcinoma, one clear cell carcinoma, one squamous carcinoma and four Brenner tumors.[138]

Müllerian tumors are not easy to distinguish from mesothelioma of the testicular tunics (Table 6.26). The epithelia of the serous tumors are immunoreactive for CA 125 and c-kit (CD117), those of the mucinous tumors for CEA and cytokeratin 20. Mesothelia react with cytokeratin antibodies but not with CEA and c-kit.

Distinguishing them from testicular teratoma is easier because of the anatomic tumor location and lack of other tissue components.

Clinical course

Swelling, palpable mass, and associated hydrocele are the main symptoms. Ca 125 in serum can be elevated. Surgically removed

Figure 6.78
Typical papillary structure with columnar epithelium of a paratesticular ovarian type cystadenoma.
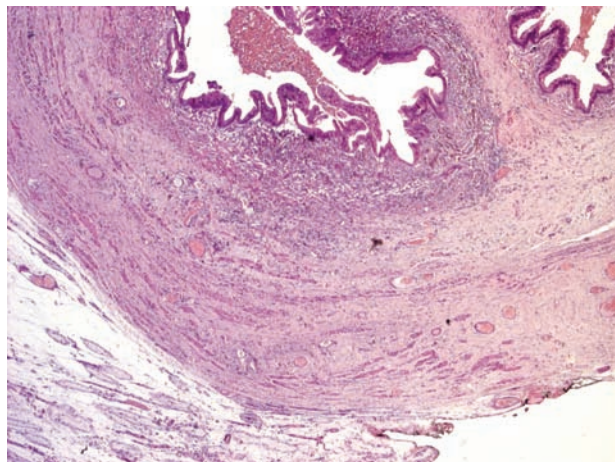
Figure 6.79
Mucinous cystadenoma borderline.

Figure 6.77
A part of an ovarian type cystadenoma of the paratesticular region.

Table 6.26 Differences between ovarian type cystadenomas/cystadenocarcinomas and mesothelioma of the tunica vaginalis testis

	Mesothelioma	Ovarian type tumors
CK7+/CK20−	~70%	100%
CEA	0%	100%
Cells	cuboidal	cylindric
Cilia	0	present
Psammoma bodies	rare	frequent
Hydrocele	>90%	rare
Asbestos exposure	25–50%	0%

borderline serous and mucinous tumors have a favorable prognosis. Cystadenocarcinomas of both types can recur and metastasize and/or show a peritoneal spread, as in their counterparts in the ovaries.[193–195]

Nephroblastoma

Nephroblastoma (Wilms tumor) can arise in testicular teratomas or intrascrotally in heterotopic renal anlage. Clinically they behave like kidney tumors; they also require the same special treatment.

Lymphoma and plasmacytoma

The isolated manifestations of lymphatic malignancies in the testis without generalized nodal manifestation are called primary testicular lymphomas and/or plasmacytomas.

Epidemiology

Lymphomas are the most frequent testicular tumors in men older then 50. Children, usually between the ages of 3 and 10, are affected less frequently. In large series lymphomas account for up to 7% of all testicular tumors or for 1–2% of all non-Hodgkin-lymphomas (NHLs).[198] In one-third of cases the manifestation is bilateral. The spread to the adjacent epididymis or spermatic cord is a common occurrence; primary lymphomas in this location are, on the other hand, very rare.

Plasmacytomas are not that common, with only 51 cases described and a wide age range (26–89 years). According to the literature,[199] a genuine primary testicular manifestation has been observed in only six cases; all other reports describe the rare testicular manifestation of a bone morrow tumor.

Neither in the series of the Armed Forces Institute of Pathology nor of the British Testicular Tumour Registry, nor in the series of the International Extranodal Lymphoma Study Group has a single case of Hodgkin disease of the testis been observed.[198,200,201]

Morphology

Lymphomas are bulky, fleshy, whitish-gray or pink colored tumors with yellow necrotic areas (Figure 6.80). In contrast to the quite similar seminomas, lymphatic tumors infiltrate the adjacent epididymis (60%) and/or spermatic cord (40%). Plasmacytomas are not fleshy but can be soft and tan to tan-white with hemorrhagic areas.

Lymphoma and plasmacytoma cells spread intertubularly in the interstitium of the testicular parenchyma (Figures 6.81, 6.82). Some few seminiferous tubules are always more or less well preserved; others are invaded by the tumor cells. Diffuse sclerosis is a common finding.

More than 80% of NHLs belong to the *diffuse large B cell type* with or without sclerosis.[198,202] Other types of the B lineage are *follicular, mantle cell, and Burkitt type* lymphomas. Nine cases of *natural killer (NK)/T cell lymphomas* which are typical for the facial area ('nasal type') affecting the testis have been reported,[203] but in one other series including 2687 NHL cases, 11% were of T (not otherwise specified) immunophenotype.[202]
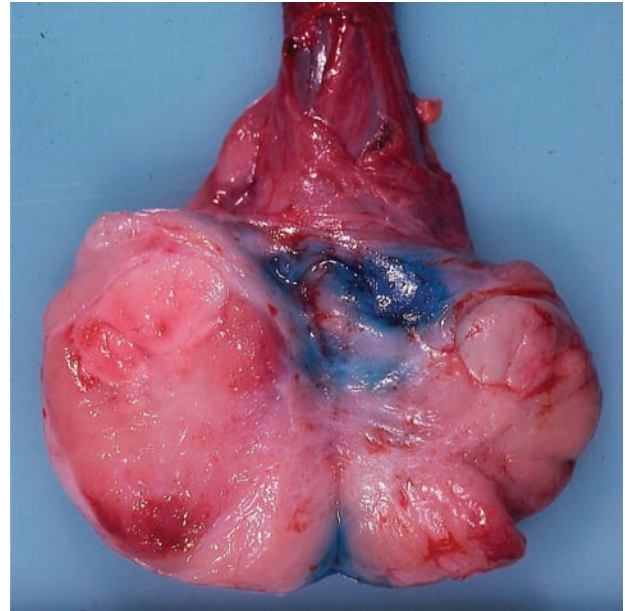
Figure 6.80
Gross appearance of a primary lymphoma of the testis.
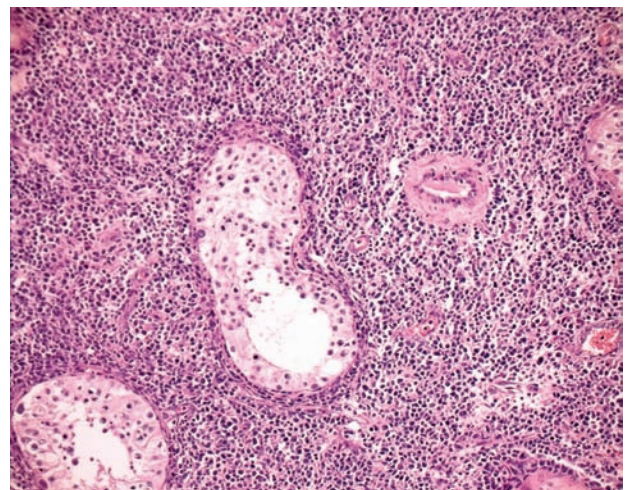
Figure 6.81
Intertubular spread of a diffuse large B cell lymphoma of the testis.

Testicular lymphomas can rarely be mistaken for germ cell tumors. Nevertheless it happens that lymphomas are confused with spermatocytic seminomas, classic seminomas, and even embryonal carcinomas. The age of the lymphoma patients and the intertubular spread (Figure 6.81 and 6.82) of the tumor cells would be two absolutely atypical features for TGCT. If necessary, the use of immunohistochemical markers of lymphatic cells helps with the clarity of the diagnosis.

Clinical features

Unilateral or bilateral rapidly enlarging testes in elderly men invariably raise the suspicion of lymphoma. The patients do not have B
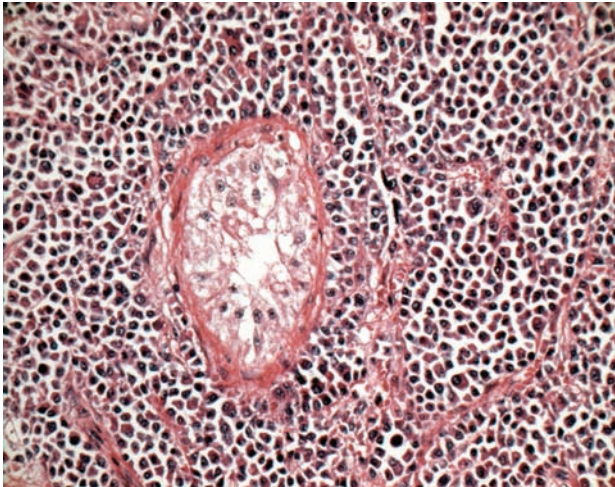
Figure 6.82
Plasmocytoma of the testis – an extremely rare testicular malignancy.

type symptoms and more than half are in Ann-Arbor stage I or II. After generalization the lymph node, the bone marrow, and, quite uncommonly, the skin and the CNS are affected. The strange relationship to the CNS remains preserved even after therapy because 15% of recurrences first affect the brain.[198] A combination of orchidectomy and chemotherapy is the standard therapy but the prognosis is poor: the median overall survival for large B cell lymphomas is less than 5 years,[198] the overall 5-year survival rate for all types of lymphomas is 17%.[202] The prognosis of plasmacytoma is even worse: median survival is 12 months.[199]

Leukemia

Post-mortem studies of leukemia cases showed an infiltration in 64% and 22% of cases with respectively acute and chronic leukemia.[204] In contrast, only 5% of living leukemia patients present a testicular enlargement. In children with acute leukemia, regardless whether myeloic or lymphocytic, the testis is more frequently affected; especially after therapy, one-third of relapses occur in the testis.[205] Extramedullary myeloid tumors (granulocytic sarcoma, chloroma) can also appear as a first clinical manifestation in the testis.[206]

The appearance to the naked eye and the intertubular spread of the leukemia cells are not different from lymphoma. The phenotypization of the cells can be tricky in case the disease is clinically unknown. The appearance of eosinophilic granulocytes is very characteristic for myeloic leukemia.

Tumors of collecting ducts and rete testis

The deep part of the rete testis – the tubuli recti – connects the two ends of the seminiferous tubule loops to the rete testis, whose channels lead to the ductuli efferentes in the caput epididymis. The channels are lined by ciliated columnar epithelium. The anatomy is the clue to the diagnosis of tumors of the collecting ducts – they must have an anatomic relationship to this small area, which is not always easy to prove.

Adenoma

Six cases of adenoma, cystadenoma, and papillary cystadenoma have been reported.[207] One case has been called sertoliform adenoma because the tumor cells were more similar to Sertoli cells than the cuboidal epithelium of the rete testis. Actually, only the location distinguishes rete adenomas from tumors of the epididymis or from a Sertoli cell tumor.[193,207] The so-called hyperplasia of rete testis encountered in cryptorchid testes and in other diseases can mimic an adenoma, the lesion, however, shows a clear continuity with the rete.[193]

Adenocarcinoma of rete testis

Epidemiology

To date, 60 cases of rete testis carcinoma have been published but probably many of these cases do not fulfill the strict diagnostic criteria required for true rete testis adenocarcinoma.[208–210] Age range is 17 to 91 years with a mean of 54.4 years and a peak incidence around the 70s. Tumors are never bilateral.

Morphology

The diameter of the described tumors ranges from 1 to 12 cm; many are multifocal and/or extending to the tunica and to the spermatic cord. Two main types of adenocarcinoma of the rete testis can be distinguished grossly and microscopically. The solid lesions (Figure 6.74) tend to be firm and rubbery, usually show a whitish cut surface, and characteristically penetrate the testis and surrounding structures. Cystic lesions recall papillary serous cystadenocarcinomas arising in the ovary and peritoneum, and they can also be multiloculated.

The morphologic criteria required for a correct diagnosis include *involvement of testicular mediastinum, transition from normal rete testis epithelium to neoplasia, intact parietal tunica vaginalis, and absence of any other primary tumor* (Table 6.27). Unfortunately this diagnosis is very popular and is often made erroneously, especially in cases of less well-differentiated gonadal stromal tumors which form gland-like structures. Cytokeratin immunohistochemistry is not very helpful because cells of stromal tumors can also stain positively.

Clinical features

Scrotal mass, in some patients present for several years, is the presenting sign in 80% of patients. About 20% feel discomfort and pain

Table 6.27 Morphologic criteria required for a correct diagnosis of rete testis carcinoma

- Involvement of testicular mediastinum
- Transition from normal rete testis epithelium to neoplasia
- Intact parietal tunica vaginalis
- Absence of any other primary tumor

Table 6.28 Testis metastases – the most frequent sites (%) of the primary tumors*

Prostate	35–60
Lung	5–15
Melanoma	9–15
Colon	5–9
Kidney	5–9
Stomach	4
Miscellaneous	1–10

*Range from different studies.

and in 30% the tumor is associated with hydrocele. In one-quarter of patients lumbar and hip pain or other systemic symptoms are caused by metastases.

The standard therapy is orchidectomy followed by retroperitoneal lymph node dissection, chemotherapy, radiotherapy, and a combination of these. Only lymph node dissection seems to be of some benefit; the value of chemotherapy is questionable and radiotherapy does not have any positive effect. The tumor spreads to the retroperitoneal lymph nodes in three-quarters and hematogenous to the lung in about one-half of cases. Other more commonly involved organs are bone, liver, and skin. The prognosis is poor with an overall 5-year survival rate of 13%. A significant prognostic factor is the size of the tumor; 75% of patients with tumors <5 cm survive the 5-year limit. The survival rate in tumors >5 cm is 0%! Adenocarcinoma of rete testis is likely to be one of the most malignant carcinomas in men.

Testicular metastases

It is rather surprising that men dying of widespread cancer only rarely have metastases in the testes. In post-mortem studies the frequency varies from 0.06 to 3.6%.[211–213] In orchidectomy specimens metastases are more frequent, however in the epididymis rather then in the testis; the figures of the British Testicular Tumour Panel and Registry were 4.5% and 0.9%, respectively.[1] The highest frequencies (6%) were shown in therapeutic orchidectomies in prostate cancer, which, however, are no longer a therapeutic procedure in this disease.[214] Other tumors which tend to metastasize to the testis are: bronchus carcinoma, melanoma, intestinal carcinomas, Merkel cell tumor, and kidney cancer (Table 6.28). Numerous case reports document, however, that any tumor can sporadically metastasize to the testis.

Metastases appear as single or multiple nodules. The microscopic spread is intertubular as in lymphomas, but invasion of the tubules is possible (Figure 6.83). Typical cancer cells are seen in the lumen of the blood vessels.

Figure 6.83
(A): Testicular metastasis of a carcinoid. (B): Epididymal metastasis of a urothelial bladder carcinoma.

Rare testicular tumors

Unusual tumors of the testis are always suspected to be secondary and not primary. Nevertheless, cases of mainly soft tissue primary tumors arising in the testis are reported sporadically in the medical literature. Since soft tissue is ubiquitous, its tumors can also appear in any part of the body. Fibromas of the tunica albuginea and hemangioma are the typical benign tumors in this location.[197,215,216] Sporadically different kinds of sarcomas including osteo- and chondrosarcomas[217,218] have been reported. Angiosarcoma can be primary[219] or the consequence of radiochemotherapy of TGCTs.[220] Even an epidermoid carcinoma developed in an epidermoid cyst has been reported.[221]

One should keep in mind that every 'primary' sarcoma can develop from a testicular teratoma, but the origin is absolutely irrelevant for the therapy, which has to be tailored to the different sarcoma types.

Epithelial tumors of the epididymis

Papillary cystadenoma of the epididymis

Papillary cystadenoma is a cystic tumor reaching the size of 5 cm in diameter. The cysts are lined by columnar cells with water-clear, glycogen-rich cytoplasm. The cells form papillae protruding in the lumen of the cysts filled with a colloid-like fluid (Figure 6.84).

Affected men seek help because of sterility due to obstructive azoospermia.[222] The tumor is rather common (18%) in men suffering from the Hippel–Lindau diseases, but it is extremely rare in sporadic cases in non-genetically stigmatized men.[223] Mutations of VHL gene (3p25–26) in tumors were, however, also found in sporadic cases.[223]

Adenocarcinoma of the epididymis

Adenocarcinomas of the epididymis also have a tubulo-papillary structure and clear cells like the adenomas, but they probably belong (with 10 plausible reported cases, age range 27–82 years) to the rarest malignancies of men.[224]

Adenomatoid tumor

Synonym: benign mesothelioma of the genital tract

Adenomatoid tumors are benign proliferations of mesothelial origin. Most reported cases arise from the epididymis; rare cases have been reported in the testicular tunica, spermatic cord, ejaculatory ducts, prostate, and suprarenal recess. Intratesticular localization is rare. Adenomatoid tumors occur in both sexes and are also found in the uterus, ovary, and fallopian tubes of the female genital tract.

Epidemiology

Adenomatoid tumor accounts for approximately 30% of all paratesticular neoplasms and is the second most common tumor after lipoma in this location.[225,226] It occurs in men with a wide range of ages, with a peak incidence between 20 and 50 years.

Morphology

Spherical tumors are markedly firm and whitish-yellow colored. The tumor size varies from a few millimeters up to 5 cm. The cuboidal tumor cells with intracytoplasmic vacuoles grow in solid cords or form pseudo-glandular structures which can be mistaken for hemangioma or even for a Sertoli cell tumor (Figure 6.86). Like all mesothelia the tumor cells are immunoreactive for all types of cytokeratin antibodies, calretinin, and vimentin (Figure 6.86).
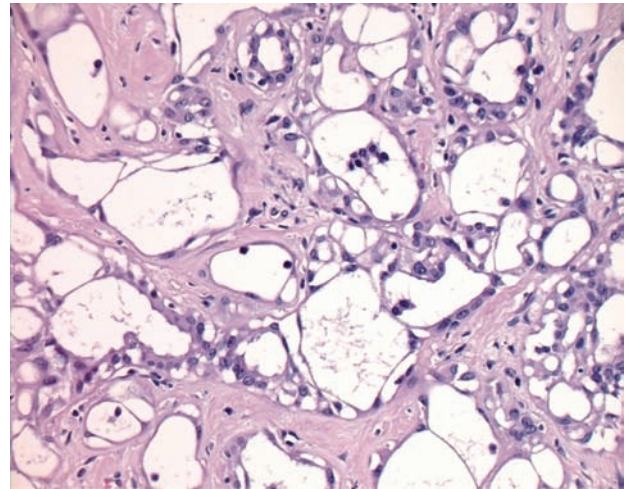
Figure 6.85
Adenomatoid tumor of the epididymis with gland-like structure lined by columnar or flattened cuboidal cells resembling epithelia.

Figure 6.84
Papillary adenoma of the epididymis: the tumor cells show typical clear water cytoplasm.
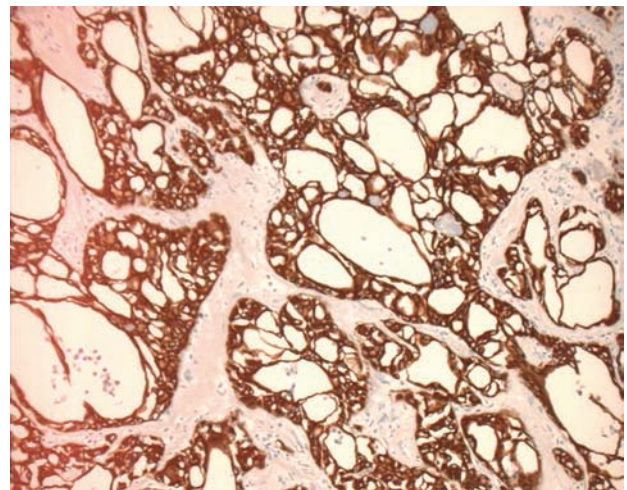
Figure 6.86
Tumor cells positively stained with calretinin, which is a marker of mesothelia. Adenomatoid tumor has also been called 'benign mesothelioma of the urogenital tract'.

Clinical course

Patients feel a painless intrascrotal nodule. The tumor is without exception benign and does not relapse.

Mesothelioma of the tunica vaginalis testis

Mesothelioma derives from mesothelia, the cells that line the serous cavities. Irrespective of the primary location, there is a well-documented association with asbestos exposure and with exceptionally poor prognoses.[227]

The WHO 2004 classification[2] of the mesotheliomas of the tunica vaginalis testis distinguishes between benign and malignant types; the benign form is further subdivided into papillary and cystic types, respectively. However, a clear-cut distinction and, even more, the prediction of the biological behavior are not always possible.

Epidemiology

According to the more than 100 case reports, mesothelioma of the tunica vaginalis testis is an extremely rare tumor. This is quite true. However, all testicular tumors are rare and in urologic centers mesotheliomas of the tunics are likely to be more frequent than other paratesticular tumors with the exception of adenomatoid tumors.

In Japan a total of 1846 (0.17%) malignant mesothelioma cases were registered among 1 056 259 autopsy cases. Of these, 68.0% were pleural mesothelioma, 24.1% peritoneal, 6.1% pericardial, and 0.3% (6 cases) located in the tunica vaginalis testis (1.6% of unknown location).[228]

Malignant mesothelioma of the tunica vaginalis testis can arise at any age; the range of the reported cases was 7 to 87 years. Almost half (47.1%), however, arose in men aged 55 to 75, but 10%[229] of patients are younger than 20.

Exposure to asbestos was confirmed in 34.2% of patients with tunics mesothelioma, but some authors argue the prevalence of exposition should be rather higher, because only in half the reported cases was there evidence of possible exposure. The higher incidence in elderly patients could be explained by a long exposure to asbestos, which is necessary for the tumor genesis.[230]

Analysis of old case reports is difficult because in the early 1950s many mesotheliomas and ovarian type cystadenomas were published under a variety of names, e.g. adenocarcinoma and/or clear cell carcinoma of the appendix testis.

Morphology

Most of the mesotheliomas of the tunica vaginalis present as a papillary exophytic in the lumen of a hydrocele sac growing tumor. The other variant shows only a more or less pronounced thickening of the tunica vaginalis with formation of small nodules (Figures 6.87, 6.88). The tumor is generally accompanied by a hydrocele, the sac of which is filled with a hemorrhagically tinged fluid.

Generally there are three types of mesotheliomas: the epithelial, the fibrous or sarcomatous, and a mixture of these two types, the biphasic type. In the tunica vaginalis the epithelial type accounts for 60.8% and the biphasic type for 37.3%, respectively. Until now, only one sarcomatous case has been reported,[231] but many other cases were probably misinterpreted as fibrosarcoma or other spindle cell malignancies. In the pre-immunohistochemical era only electron microscopy was capable of revealing the mesothelial origin of such tumors.[232]

Even so-called benign papillary mesotheliomas show the invasion of the wall of the tunic in one-quarter of cases, and another fifth infiltrate to the testis. The only really benign mesothelioma is the cystic type, which consists of a multilocular cyst lined by mesothelia. However, this tumor has been described only twice in this location.[233]

Benign reactive mesothelial proliferations in hydroceles may look histologically worrisome and are one of the main differential diagnoses.[234] Such proliferations are nonetheless circumscribed, never
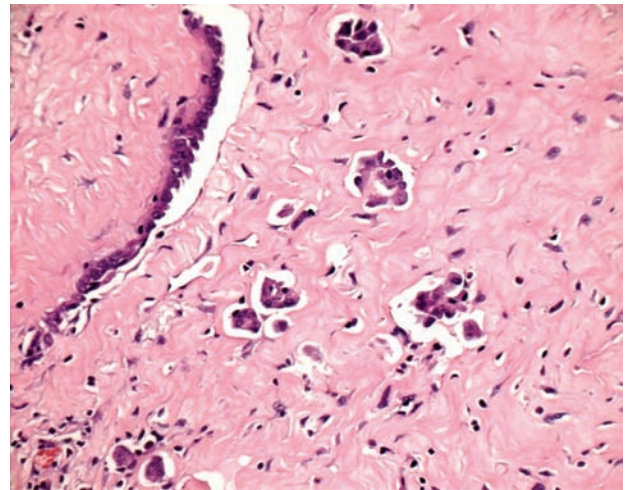
Figure 6.87
Tubular epithelial mesothelioma in the thickened tunica vaginalis.
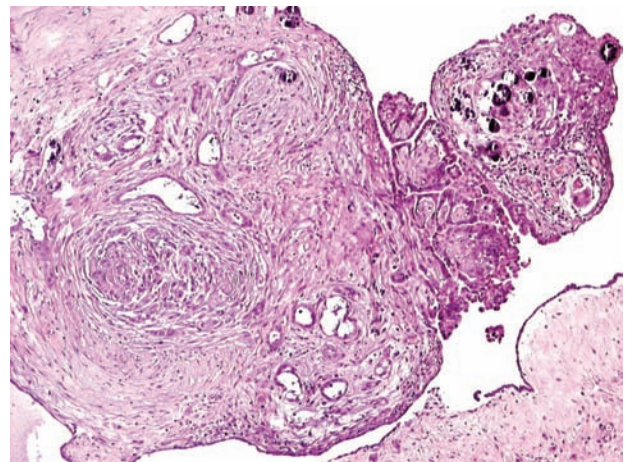
Figure 6.88
Papillary mesothelioma of the tunica vaginalis testis.

macroscopically visible, and always accidentally microscopically discovered in the wall of a resected hydrocele. Mesotheliomas, on the other hand, are always macroscopically visible.

As already mentioned, epithelial mesotheliomas can also be mistaken for ovarian type cystadenomas or carcinomas, which, however, have another anatomic location and a different immunophenotype.

Cytogenetics

The commonly (80%) aneuploid tumors show characteristic losses of chromosomes 9p, 22q, 4p, 4q, 14q, and 1p, and gains of 8q and 1q.[235]

Tumor spread

The tumor spreads locally but after local recurrence more than 80% have disseminated tumor progression. Lymph nodes are involved in about 24%, the lungs in 10%, and the liver in 5% of cases. Other described sites of metastases are pleura, colon, spleen, mesentery, omentum, and mediastinum.

Clinical features

Symptomatic hydrocele is the main symptom observed in more than half of the cases. In a further third of cases a palpable lump suggests the diagnosis of a tumor. The symptoms can also mimic epididymitis, scrotal hernia, spermatocele, and trauma.[229] Cytology of hydrocele fluid is only rarely diagnostic. In almost all cases, diagnosis is made during hydrocele surgery. Hemorrhagic fluid, a thickening of the tunica, or an overt papillary tumor raise the suspicion of it being more than a harmless hydrocele.

After surgical therapy, adjuvant chemotherapy or adjuvant radiotherapy, or a combination of both, has been used in the past with poor results. Patients with radical orchidectomy have a lower number of recurrences (14%) than those with local tumor resection (35%). Some few patients with localized disease have survived for more than 10 years, but the majority died within 5 years after diagnosis, with a median survival of approximately 23 months.[236] Localized disease and patient age below 60 are markers of a favorable outcome.[229]

Melanotic neuroectodermal tumor of infancy

Synonyms: congenital melanocarcinoma, retinal anlage tumor, pigmented congenital epulis, melanotic progonoma

Melanotic neuroectodermal tumor of infancy (MNTI) is a rare neoplasm with about 350 cases reported since the first description in 1918.[237] Most commonly, the lesion affects the maxilla of infants during the first year of life, but it may also occur in the mandible, skull, brain, epididymis, and other rare locations. To date, 20 cases have been described in the epididymis and 1 in the testis of a 17-year old man, where MTNI was the predominant part of a teratoma.[238] The other patients were all younger than 10 years (range 4 months to 8 years).

The tumor is circumscribed and cream-colored with black spots. It is composed of mainly two cell types: small immature neuroblast-like cells and large columnar or cuboidal epithelial-like cells with or without melanin granules. In amelanotic cells melanin can be made visible with special stains (Masson Fontana stain).

Clinically, hydrocele can accompany the palpable tumor.[238] In some cases elevated values of AFP in serum, and vanilmandelic and homovanilic acid in urine, can be detected. To date lymph node metastases have been described in three cases.

Desmoplastic small round cell tumor

Desmoplastic small round cell tumor is a rare, primarily intra-abdominal tumor that has a poor outcome with current therapies. There have until now been 10 cases located either in the tunica vaginalis or in the recess between the rete testis and epididymis.[239] The tumor is firm and tan. Microscopically the tumor consists of the typical 'small round blue' cells which means that they have a prominent round nucleus with finely dispersed chromatin and a small rim of cytoplasm (Figure 6.89). Tumor cell nests are surrounded by desmoplastic stroma. There is a distinctive immunophenotype, specifically positive for keratin, vimentin, desmin, and neuron-specific enolase, as well as a characteristic chromosomal abnormality, the EWS/WT-1 fusion transcript t(11,22)(p13,q12).

The tumor metastasizes intra-abdominally and to the lung. It shows a certain degree of chemosensitivity but, despite aggressive treatments, survival rates remain low.

Soft tissue tumors of the spermatic cord

Theoretically any kind of soft tissue tumor can arise in the spermatic cord; nevertheless, they are rare in this anatomic location. *Lipomas,*
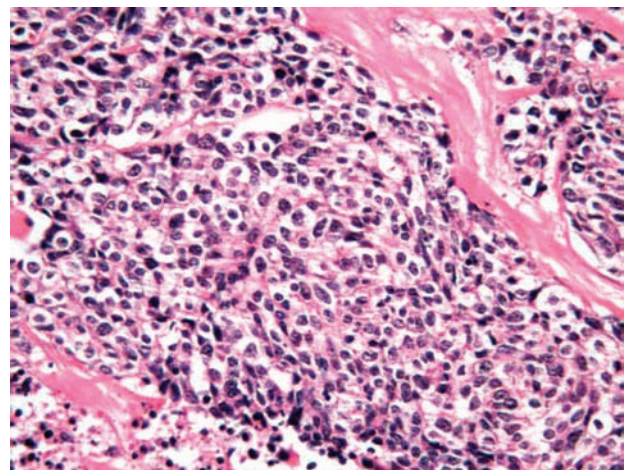
Figure 6.89
Desmoplastic small round cell tumor of the testis; the typical small, round, and blue cells are surrounded by a desmoplastic stroma (by courtesy of Prof Ferran Algaba, Barcelona).

leiomyomas, hem- and lymphangiomas as well as, less frequently, neurofibromas are benign tumors encountered in this region. *Lipo- and leiomyosarcomas* are the malignant counterpart affecting adult men (Figures 6.90, 6.91).

Of juvenile *rhabdomyosarcomas*, 25% (average age 6.6 years) arise in this location.[240] The *spindle cell type* in particular has a predilection for the paratesticular region; 38% of them are located here.

Aggressive angiomyxoma is a rare, locally infiltrative tumor usually arising in the pelvic and perineal soft tissues of young women. Nevertheless, 39 cases involving scrotum, spermatic cord, inguinal region, and perineum of men have recently been described.[241] Aggressive angiomyxoma has a high rate of local recurrence because of its infiltrative growth and anatomic location, making complete excision with wide margins difficult.
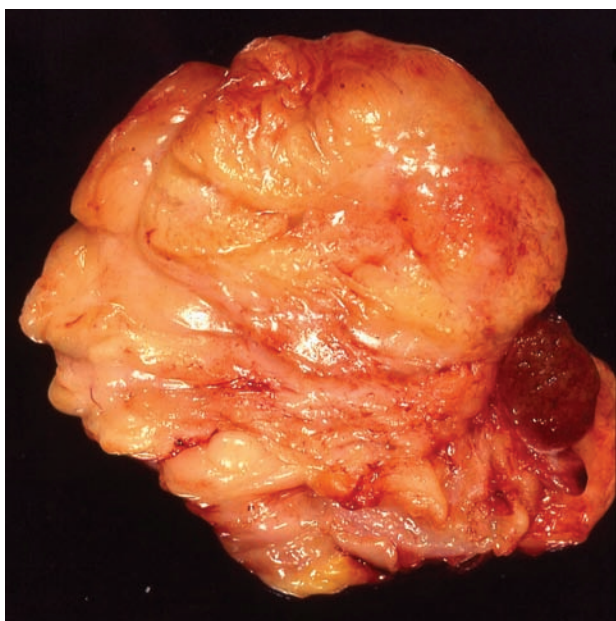
Figure 6.90
Gross appearance of an atypical lipoma of the spermatic cord.
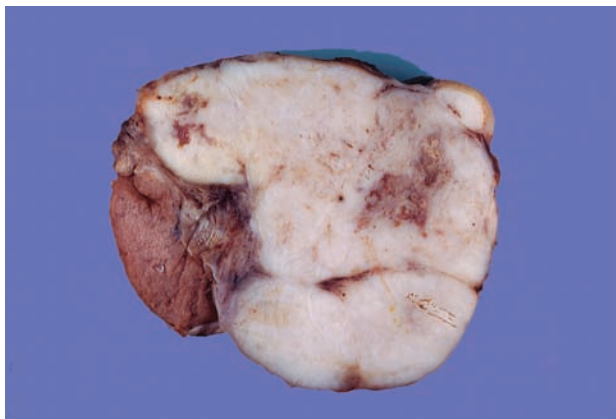
Tumor-like lesions

Many non-neoplastic lesions can cause a mass in the scrotum or testicular swelling and have gross and, rarely, also microscopic features simulating a neoplasia (Table 6.29).

Ectopic adrenal tissue appears in the form of small yellow nodules (Figure 6.92) which can be found somewhere along the spermatic cord (Figure 6.82), epididymis, rete testis, and tunica albuginea in 10%.[242]

Cysts of the tunica albuginea are lined by mesothelia and often diagnosed by ultrasound.

Cystic dysplasia of the rete testis is a very rare cause of a pediatric scrotal mass, often associated with renal and other genitourinary tract anomalies. The lesion consists of multiple, anastomosing, irregular cystic spaces of varying sizes and shapes predominantly located in the region of the rete testis. The cysts can enlarge and displace the testicular parenchyma.[243]

Nodular precocious maturation – testotoxicosis is a form of male sexual precocity characterized by active Leydig cell differentiation and premature onset of spermatogenesis in the absence of pituitary gonadotropin stimulation (Figure 6.93). Testes show a diffuse or nodular enlargement due to Leydig cell maturation and proliferation.[244]

Table 6.29 Tumor-like lesions

Ectopic adrenal tissue
Cysts of the tunica albuginea
Cystic dysplasia of the rete testis
Nodular precocious maturation – testotoxicosis
Pseudogranulomatous orchitis
Malkoplakia
Fibromatous (nodular) periorchitis
Myxofibromatous inflammatory pseudotumor
Sclerosing lipogranuloma
Cholesterol granuloma
Infarcts and hematomas
Sperm granuloma of the epididymis and vas deferens
Vasitis and epididymitis nodosa
Splenogonadal fusion
Hepatogonadal fusion
Lipomatosis testis – Cowden disease

Figure 6.91
Malignant fibrous histiocytoma of the spermatic cord.
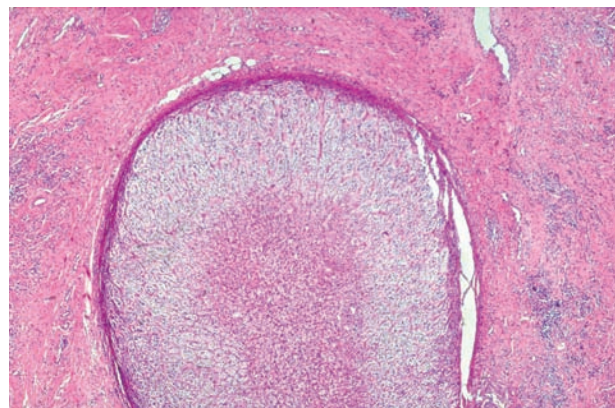
Figure 6.92
Small ectopic adrenal gland in the spermatic cord.

Orchitis: due to the general symptoms of inflammation, orchitis does not always simulate a tumor. But granulomatous forms with slow onset, like syphilis or leprosy, which leads to fibrosis and indurations of the organ, might be mistaken for neoplasia. In particular the so-called 'idiopathic granulomatous orchitis' is clinically indistinguishable from a testicular tumor. It affects men in the 5th and 6th decade with a history of urinary infection (Figure 6.94). The testicular parenchyma is replaced by a tan-yellow mass which resembles seminoma. Microscopically the more or less destroyed tubules are filled with macrophages which give the lesion the appearance of a granuloma.[146] A special form is the 'malkoplakia', which is grossly not very different from the pseudogranulomatous orchitis. Microscopically the tissue is replaced by large epitheloid cells with eosinophilic cytoplasm containing sometimes targetoid basophilic inclusions called Michaelis Gutman bodies (Figure 6.51).[245, 246]

Fibromatous (nodular) periorchitis is a benign reactive myofibroblastic proliferation, which, although extremely rare, is probably the second most frequent benign paratesticular lesion after adenomatoid tumor.[247] The tumor presents as multiple fibrotic plaques with a diameter of 0.5–8 cm, or as true stony nodules, which can detach and lie free as 'corpora libera' in the tunica vaginalis (Figure 6.95). Microscopically the lesion consists of the 'florid' phase of proliferating fibroblasts, or myofibroblasts with scanty inflammatory cells. The nodules are built of hyalinized collagen, sometimes with patchy calcifications.

The painless lesion can occur at any age, but only four cases have been reported in men younger then 18 years.[248] More than half of the cases are associated with hydrocele and one-third have a history of trauma or orchitis.

Myxofibromatous inflammatory pseudotumor has a very similar morphology and probably both lesions only represent two extremes of a broad morphologic spectrum of reactive, inflammatory tissue reactions. It is hardly surprising that in the literature these lesions are confused. Grossly the pseudo-tumor is similar to the nodular periorchitis, but the histologic characteristic is a myxomatous proliferation of myofibroblasts with inflammatory cells and a conspicuous vascularization resembling granulation tissue (Figure 6.96).

Figure.6.93
Testotoxicosis: diffuse Leydig cell proliferation and maturation of the seminiferous tubules in a 4-year-old boy with clinical signs of sexual precocity (by courtesy of Professor Kurt W Schmid, Essen).

Figure 6.95
A free-lying detached stony nodule ('corpus liberum') in the tunica vaginalis.
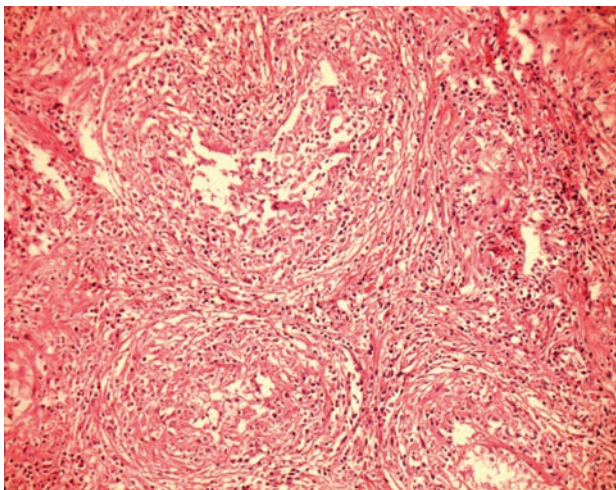
Figure 6.94
Granulomatous orchitis: tubules filled with macrophages give the impression of granuloma.
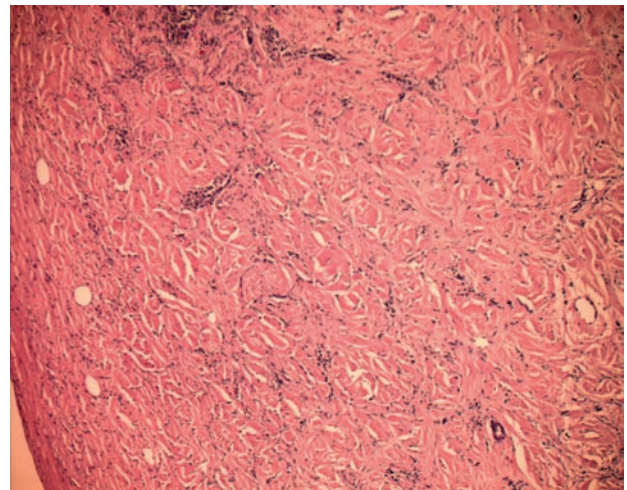
Figure 6.96
Fibromatous periorchitis with proliferating fibroblast and scanty inflammatory cells.

Sclerosing lipogranuloma is a locally reactive process following injury to adipose tissue. In some older cases, the lesion followed lipid injection for enhancing the size of the genitalia,[249] but in recent cases the patient did not have a history of such therapy.[250] Characteristically, the lesion shows a broad coagulative and lytic necrosis with many epithelioid granulomas, which contain multinucleated giant cells of foreign body and Langhans' types.

Cholesterol granuloma[251] is a rare foreign body inflammatory reaction of tunica vaginalis that may simulate an intrascrotal tumor on physical examination, on ultrasound, and at operation. The lesion can be caused by trauma or inflammation, since cholesterol crystal deposits are often seen after purulent inflammation.

Infarcts and hematomas lead to sudden testicular swelling. The cause of hemorrhagic infarction in young men is commonly a testicular torsion. Hematomas are the consequence of trauma or of vasculitis which can be localized in the testis or a manifestation of generalized disease. Polyarteriitis nodosa and Wegener's granulomatosis have been described in the testis, but the manifestation of Henoch–Schonlein purpura in this organ seems to be the most common type of vasculitis in the testis.[252]

Sperm granuloma of the epididymis and vas deferens is a granulomatous reaction caused by the extravasation of sperm, which produces a painful intrascrotal nodule.[253] The majority of such granulomas are related to vasectomy and, thus, 90% are localized in the vas deferens, the remaining 10% in the epididymis.

Vasitis and epididymitis nodosa is a lesion typical in men who have undergone vasectomy. It is characterized microscopically by multiple small ductules extending from the central lumen of the vas into the muscle layers and adventitia (Figure 6.97).[254] Localization in the epididymis is uncommon.[255] Caveat, the lesion can be mistaken for adenocarcinoma!

Splenogonadal fusion is a fusion of the developing splenic anlage and the gonadal mesoderm at approximately week 5 of intra-uterine life. It commonly presents as a testicular mass treated with an unnecessary orchidectomy. More than 120 cases of splenogonadal fusion have been reported,[256] in contrast to *hepatogonadal fusion* which was observed in only two cases, although one of them was an intra-abdominal testis attached to the lower lateral part of the right lobe.[257]
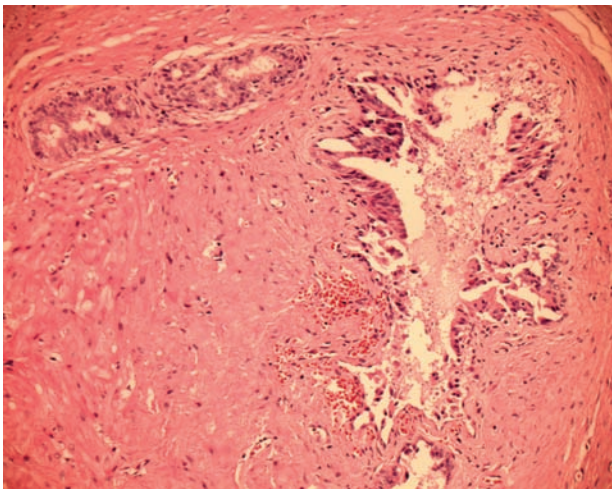
Lipomatosis testis – Cowden disease – is a rare condition defined by multiple hamartomatous growths and a high risk of cancer development. The syndrome is inherited as an autosomal dominant trait. The PTEN/MMAC1/TEP1 tumor suppressor gene on chromosome 10q23.3 has proven to contain a germline mutation predisposing for uncontrolled cell growth. Patients have hyperechoic lesions in the ultrasound investigation. Microscopically, multiple foci of fat tissue called lipomatosis testis have been found in testicular interstitium.[258]

Handling and reporting surgical specimens of testicular cancer

Once removed, the *partial or radical orchidectomy specimen* should be immediately transferred to the pathology department, preferably fresh. Although most molecular investigations can also be carried out in paraffin-embedded material, fresh material doubtless has certain advantages for this kind of investigation. The urologist should not incise the specimen, due to possible contamination of resection margins. In case immediate transfer is not possible, the specimen should be placed in formalin to fix. Even in such cases it is better not to incise the tunica albuginea, because the testicular parenchyma everts due to the fixation and makes the gross assessment of the local relationship of the tumor difficult.[259]

The pathologist measures the length of the spermatic cord and the long and short diameter of the testis. The resection margin from the top of the spermatic cord is cut and put into a cassette for further histologic processing. The specimen is then bivalved through the testis and epididymis, enabling the pathologist to describe the location, color, and consistency, and to measure the area of the tumor. The presence or absence of invasion into the tunica albuginea, epididymis, and spermatic cord should be recorded. Then the testis is sliced along its long axis parallel to the initial section at about 3 mm intervals. The sampling of tumor tissue comprises at least one block of tumor per cm of diameter (minimum 6 blocks). In addition, samples of hemorrhagic areas, tumor edge with adjacent normal-appearing tissue, areas of tumor closest to tunic, rete, epididymis, and cord should be submitted for histology.

The histologic report should include not only the diagnosis and TNM stage. According to the presence or absence of morphologic variables that affect prognosis, patients should be divided into low- and high-risk groups (for exemple: *Mixed germ cell tumor: embryonal carcinoma (80%) + yolk sac tumor (5%) + teratoma (15%) 2+ vascular invasion (pT2)= high-risk patient*).

Lymphadenectomy specimens are also transported fresh or formalin-fixed to the pathology lab. The number and dimension of lymph nodes are recorded. The lymph nodes are sectioned along the long axis and both halves processed.

Residual masses after chemotherapy are inked to assess the completeness of the resection and then sliced at 3 mm intervals. Blocks of different macroscopic areas, or preferably the entire specimen, are processed and investigated.

Testicular biopsies for IGCNU diagnosis should be put in formalin, since immunohistochemical methods are based on formalin fixation. Biopsy fixation in Bouin's (or Steve's, Davidson's) fluid is, however, mandatory for the investigation of infertility. For the detection of atypical germ cell PSA or immunohistochemical staining, PIAP and CD 117 are recommended.

Figure 6.97
Vasitis nodosa: a peculiar ductular proliferation in the wall of the vas deferens.

References

1. Pugh RCB. Testicular tumors–introduction. In: Pugh RCB, ed. Pathology of the Testis. Oxford, London, Edinburgh Melbourne: Blackwell Scientific Publications: 1976; 139–59.

2. Eble JN, Sauter G, Epstein JI, Sesterhenn IA, eds. WHO Classification of tumors. Pathology & Genetics. Tumors of the Urinary System and Male Genital Organs. Lyon, France: IARCPress; 2004; 218–9.

3. Collins DH, Pugh RC. Classification and frequency of testicular tumors. Br J Urol 1964; 36 (Suppl): 1–11.

4. Skakkebaek NE. Possible carcinoma in situ of the testis. Lancet 1972; 2: 516–17.

5. Mostofi FK, Sobin LH. Histological Typing of Tumors of the Testis. International Histological classification of tumors, No 16. Geneva, Switzerland: WHO, 1977.

6. von Hochstetter AR, Hedinger CE. The differential diagnosis of testicular germ cell tumors in theory and practice. A critical analysis of two major systems of classification and review of 389 cases. Virch Arch A Pathol Anat Histol 1982; 396: 247–77.

7. Stiens R. Testikuläre Keimzelltumoren: Histologie, Klassifikation, Pathologie und Häufigkeit. In: Weißbach L, Hildenbrand G, eds. Register und Verbundstudie für Hodentumoren–Bonn. Ergebnisse einer prospektiven Untersuchung. München: W Zuckschwerdt Verlag, 1982; 27–50.

8. Jacobsen KG, Barlebo H, Olsen J et al. Testicular germ cell tumors in Denmark 1976–1980. Pathology of 1058 consecutive cases. Acta Radiol Oncol 1984; 23: 239–47.

9. Horwich A, Shipley J, Huddart R. Testicular germ-cell cancer. Lancet. 2006; 367: 754–65.

10. Rajpert-De Meyts E. Developmental model for the pathogenesis of testicular carcinoma in situ: genetic and environmental aspects. Hum Reprod Update 2006; 12: 303–23.

11. Almstrup K, Ottesen AM, Sonne SB et al. Genomic and gene expression signature of the pre-invasive testicular carcinoma in situ. Cell Tissue Res 2005; 322: 159–65.

12. Kraggerud SM, Berner A, Bryne M et al. Spermatocytic seminoma as compared to classical seminoma: an immunohistochemical and DNA flow cytometric study. APMIS 1999; 107: 297–302.

13. Giwercman A, Cantell L, Marks A. Placental-like alkaline phosphatase as a marker of carcinoma-in-situ of the testis. Comparison with monoclonal antibodies M2A and 43–9F. APMIS 1991; 99: 586–94.

14. Skotheim RI, Lothe RA. The testicular germ cell tumor genome. APMIS 2003; 111: 136–50.

15. Spierings DC, de Vries EG, Vellenga E et al. The attractive Achilles heel of germ cell tumors: an inherent sensitivity to apoptosis-inducing stimuli. J Pathol. 2003; 200: 137–48.

16. Ferlay J, Bray F, Pisani P et al. GLOBOOCAN 2002 Cancer Incidence, Mortality and Prevalence Worldwide. Lyon, France: IARC Press; 2004.

17. Purdue MP, Devesa SS, Sigurdson AJ et al. International patterns and trends in testis cancer incidence. Int J Cancer 2005; 115: 822–7.

18. McGlynn KA, Devesa SS, Sigurdson AJ et al. Trends in the incidence of testicular germ cell tumors in the United States. Cancer 2003; 97: 63–70.

19. McGlynn KA, Devesa SS, Graubard BI et al. Increasing incidence of testicular germ cell tumors among black men in the United States. J Clin Oncol 2005; 23: 5757–61.

20. Leonard MP, Jeffs RD, Leventhal B et al. Pediatric testicular tumors: the Johns Hopkins experience. Urology 1991; 37: 253–6.

21. Dieckmann KP, Pichlmeier U. Clinical epidemiology of testicular germ cell tumors. World J Urol 2004; 22: 2–14.

22. Herrinton LJ, Zhao W, Husson G. Management of cryptorchism and risk of testicular cancer. Am J Epidem 2002; 157: 602–5.

23. Moller H, Prener A, Skakkebaek NE. Testicular cancer, cryptorchidism, inguinal hernia, testicular atrophy, and genital malformations: case control studies in Denmark. Cancer Causes Control 1996; 7: 264–74.

24. Pike MC, Chilvers C, Peckham MJ. Effect of age at orchidopexy on risk of testicular cancer. Lancet 1986; 1: 1246–8.

25. Raina V, Shukla NK, Gupta NP et al. Germ cell tumors in uncorrected cryptorchid testis at Institute Rotary Cancer Hospital, New Delhi. Br J Cancer 1995; 71: 380–2.

26. Skakkebaek NE, Rajpert-De Meyts E, Main KM. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. Hum Reprod 2001; 16: 972–8.

27. Den Hond E, Schoeters G. Endocrine disrupters and human puberty. Int J Androl 2006; 29: 264–71.

28. Sharp RM. The 'oestrogen hypothesis'–where do we stand now? Int J Androl 2002; 26: 2–15.

29. Tabernero J, Paz-Ares L, Salazar R et al. Incidence of contralateral germ cell testicular tumors in South Europe: report of the experience at 2 Spanish university hospitals and review of the literature. J Urol 2004; 171: 164–7.

30. Czene K, Lichtenstein P, Hemminki P Enviromental and heritable causes of cancer among 9.6 milllion individuals in the Swedish Family–Cancer Database. Int J Cancer 2002; 99: 260–6.

31. Hemminki K, Chen B. Familial risks in testicular cancer as aetiological clues. Int J Androl 2006; 29: 205–10.

32. Heimdal K, Olsson H, Tretli S et al. Familial testicular cancer in Norway and southern Sweden. Br J Cancer 1996; 73: 964–9.

33. Rapley EA, Crockford GP, Easton DF et al. International Testicular Cancer Linkage Consortium. Localisation of susceptibility genes for familial testicular germ cell tumor. APMIS 2003; 111: 128–33.

34. Manuel M, Katayama PK, Jones HW Jr. The age of occurrence of gonadal tumors in intersex patients with a Y chromosome. Am J Obstet Gynecol 1976; 124: 293–300.

35. Nathanson KL, Kanetsky PA, Hawes R et al. The Y deletion gr/gr and susceptibility to testicular germ cell tumor. Am J Hum Genet 2005; 77: 1034–43.

36. Fend F, Hittmair A, Rogatsch H et al. Seminomas positive for Epstein–Barr virus by the polymerase chain reaction: viral RNA transcripts (Epstein–Barr-encoded small RNAs) are present in intratumoral lymphocytes but absent from the neoplastic cells. Mod Pathol 1995; 8: 622–5.

37. Guo J, Pukkala E, Kyyronen P et al. Testicular cancer, occupation and exposure to chemical agents among Finnish men in 1971–1995. Cancer Causes Control 2005; 16: 97–103.

38. Mills PK, Newell GR, Johnson DE. Testicular cancer associated with employment in agriculture and oil and natural gas extraction. Lancet 1984; 1: 207–10.

39. Davies JM. Testicular cancer in England and Wales: some epidemiological aspects. Lancet 1981; 1: 928–32.

40. Pukkala E, Weiderpass E. Socio-economic differences in incidence rates of cancers of the male genital organs in Finland, 1971–95. Int J Cancer 2002; 102: 643–8.

41. Kim B, Winter TC 3rd, Ryu JA. Testicular microlithiasis: clinical significance and review of the literature. Eur Radiol 2003; 13: 2567–76.

42. Loy V, Dieckmann KP. Prevalence of contralateral testicular intraepithelial neoplasia (carcinoma in situ) in patients with testicular germ cell tumor. Results of the German multicentre study. Eur Urol 1993; 23: 120–2.

43. Sigg C, Hedinger CE. Atypical germ cells of the testis. Comparative ultrastructural and immunohistochemical investigations. Virch Arch [A] 1983; 402: 439–50.

44. Dieckmann KP, Skakkebaek NE. Carcinoma in situ of the testis: review of biological and clinical features. Int J Cancer 1999; 83: 815–22.

45. Armstrong GR, Buckley CH, Kelsey AM. Germ- cell expression of placental alkaline phosphatase in male pseudohermaphroditism. Histopathology 1991; 18: 541–7.

46. Coffin CM, Ewing S, Dehner LP. Frequency of intratubulär germ cell neoplasia with invasive germ cell tumors. Histologic and immunocytochemical features. Arch Pathol Lab Med 1985; 109: 555–9.

47. Daugaard G, von der Maase H, Olsen et al. Carcinoma-in-situ testis in patients with assumed extragonadal germ-cell tumors. Lancet 1987; 2: 528–30.

48. Hailelemariam S, Engler DS, Bannwart F et al. Primary mediastinal germ cell tumor with intratubulär germ cell neoplasia of the testis–further support for germ cell origin of these tumors: a case report. Cancer 1997; 79: 1031–6.

49. el-Naggar AK, Ro JY, McLemore D et al. DNA ploidy in testicular germ cell neoplasms. Histogenetic and clinical implications. Am J Surg Pathol 1992; 16: 611–18.

50. Looijenga LH, Rosenberg C, van Gurp RJ et al. Comparative genomic hybridization of microdissected samples from different stages in the development of a seminoma and a non-seminoma. J Pathol 2000; 191: 187–92.

51. Rosenberg C, Van Gurp RJ, Geelen E et al. Overrepresentation of the short arm of chromosome 12 is related to invasive growth of human testicular seminomas and nonseminomas. Oncogene 2000; 19: 5858–62.

52. von der Maase H, Rorth M, Walbom-Jorgensen S et al. Carcinoma in situ of contralateral testis in patients with tesicular germ cell cancer: study of 27 cases in 500 patients. Br Med J 1986; 293: 1398–401.

53. Dieckmann KP, Loy V, Buttner P. Prevalence of bilateral testicular germ cell tumors and early detection based on contralateral intra-epithelial neoplasia. Br J Urol 1993; 71: 340–5.

54. Dieckmann KP, Classen J, Loy V. Diagnosis and management of testicular intraepithelial neoplasia (carcinoma in situ)–surgical aspects. APMIS 2003; 111: 64–8.

55. Grigor KM, Rorth M. Should the contralateral testis be biopsied? Round table discussion. Eur Urol 1993; 23: 129–35.

56. Herr HW, Sheinfeld J. Is biopsy of the contralateral testis necessary in patients with germ cell tumors? J Urol 1997; 158: 1331–4.

57. Christensen TB, Daugaard G, Geertsen PF et al. Effect of chemotherapy on carcinoma in situ of the testis. Ann Oncol 1998; 9: 657–60.

58. McGlynn KA, Devesa SS, Sigurdson AJ et al. Trends in the incidence of testicular germ cell tumors in the United States. Cancer 2003; 97: 63–70.

59. Kay R. Prepubertal testicular tumor registry. J Urol 1993; 150: 671–4.

60. Thackray AC, Crane WAJ. Seminoma. In: Pugh RCB, eds. Pathology of the Testis, Oxford London, Edinburgh Melbourne: Blackwell Scientific Publications, 1976; 164–98.

61. Mikuz G, Kiesler J, Scheiber K et al. Morphology and incidence of testicular tumors in western Austria (1945–1980). Zentralbl Allg Pathol 1984; 129: 91–100.

62. von Hochstetter AR Mitotic count in seminomas–an unreliable criterion for distinguishing between classical and anaplastic types. Virch Arch [A] 1981; 390: 63–9.

63. Damjanov I, Niejadlik DC, Rabuffo JV et al. Cribriform and sclerosing seminoma devoid of lymphoid infiltrates. Arch Pathol Lab Med 1980; 104: 527–30.

64. Young RH, Finlayson N, Scully RE Tubular seminoma. Report of a case. Arch Pathol Lab Med 1989; 113: 414–16.

65. Mostofi FK, Sesterhenn IA. Pathology of germ cell tumors of testes. Prog Clin Biol Res 1985; 203: 1–34.

66. Zuckman MH, Williams G, Lewin HS. Mitosis counting in seminoma: an exercise of questionable significance. Hum Pathol 1980; 19: 329–35.

67. Hori K, Uematsu K, Yasoshima H et al. Contribution of cell proliferative activity to malignancy potential in testicular seminoma. Pathol Int 1997; 47: 282–7.

68. http://www.Immunoquery.com (Immunohistochemistry Literature Database Query System).

69. Hittmair A, Rogatsch H, Hobisch A et al. CD30 expression in seminoma. Hum Pathol 1996; 27: 1166–71.

70. Hittmair A, Rogatsch H, Feichtinger H et al. Testicular seminomas are aneuploid tumors. Lab Invest 199; 72: 70–4.

71. van Echten J, Osterhuis JW, Looijenga LH et al. No recurrent structural abnormalities apart from i(12p) in primary germ cell tumors of the adult testis. Genes Chromosomes Cancer 1995; 14: 133–44.

72. Castedo SM, de Jong B, Osterhuis JW et al. Cytogenetic analysis of human seminomas. Cancer Res 1989; 49: 5696–570.

73. Warde P, Specht L, Horwich A et al. Prognostic factors for relapse in stage I seminoma managed by surveillance: a pooled analysis. J Clin Oncol 2002; 20: 4448–52.

74. Tyldesley S, Voduc D, McKenzie M et al. Surveillance of stage I testicular seminoma: British Columbia Cancer Agency Experience 1992 to 2002. Urology 2006; 67: 594–8.

75. Parker C, Milosevic M, Panzarella T et al. The prognostic significance of the tumor infiltrating lymphocyte count in stage I testicular seminoma managed by surveillance. Eur J Cancer 2002; 38: 2014–19.

76. Josefsen D, Fossa S. The management strategies for stage I seminoma. Clin Oncol (R Coll Radiol) 2005; 17: 539–42.

77. Aparicio J, Germa JR, Garcia del Muro X et al. Risk-adapted management for patients with clinical stage I seminoma: the Second Spanish Germ Cell Cancer Cooperative Group study. J Clin Oncol 2005; 23: 8717–23.

78. Hernes EH, Harstad K, Fossa SD. Changing incidence and delay of testicular cancer in southern Norway (1981–1992). Eur Urol 1996; 30: 349–57.

79. Patterson H, Norman A, Mitra SS et al. Combination carboplatin and radiotherapy in the managment of Stage II testicular seminoma: comparison with radiotherapy alone. Radiother Oncol 2001; 59: 5–11.

80. Masson P, Étude sur le séminome. Rev Canad Biol 1946; 5: 361–87.

81. Jacobsen GK, Barlebo H, Olsen J et al. Testicular germ cell tumors in Denmark 1976–1980. Pathology of 1058 consecutive cases. Acta Radiol Oncol 1984; 109: 938–42.

82. Eble JN. Spermatocytic seminoma. Hum Pathol 1994; 25: 1035–42.

83. Talerman A. Spematocytic seminoma: clinicopathological study of 22 cases. Cancer 1980; 45: 2169–76.

84. Verdorfer I, Rogatsch H, Tzankov A et al. Molecular cytogenetic analysis of human spermatocytic seminomas. J Pathol 2004; 204: 277–81.

85. Burke AP, Mostofi FK. Placental alkaline phosphatase immunohistochemistry of intratubular malignant germ cells and associated testicular germ cell tumors. Hum Pathol 1988; 19: 663–70.

86. Rosai J, Khodadoust K, Silber I. Spermatocytic seminoma. II. Ultrastructural study. Cancer 1969; 24: 103–16.

87. Albores Saavedra J, Huffman H, Alvarado-Cabrero I et al. Anaplastic variant of spermatocytic seminoma. Hum Pathol 1996; 27: 650–5.

88. Kraggerud SM, Berner A, Bryne M et al. Spermatocytic seminoma as compared to classical seminoma: an immunohistochemical and DNA flow cytometric study. APMI 1999; 107: 297–302.

89. Cummings OW, Ulbright TM, Eble JN et al. Spermatocytic seminoma: an immunohistochemical study. Hum Pathol 1994; 25: 54–9.

90. Steiner H, Gozzi C, Verdorfer I et al. Metastatic spermatocytic seminoma–an extremely rare disease. Eur Urol 2006; 49: 183–6.

91. Chung PW, Bayley AJ, Sweet J et al. Spermatocytic seminoma: a review. Eur Urol 2004; 45: 495–8.

92. Moriyama N, Daly JJ, Keating MA et al. Vascular invasion as a prognosticator of metastatic disease in nonseminomatous germ cell tumors of the testis. Importance in 'surveillance only' protocols. Cancer 1985; 56: 2492–8.

93. Delozier-Blanchet CD, Walt H, Engel E et al. Cytogenetic studies of human testicular germ cell tumors. Int J Androl 1987; 10: 69–77.

94. Spiess PE, Brown GA, Liu P et al. Predictors of outcome in patients undergoing postchemotherapy retroperitoneal lymph node dissection for testicular cancer. Cancer 2006; 107: 1483–90.

95. Mostofi FK, Sesterhenn IA, Davis CJ Jr. Developments in histopathology of testicular germ cell tumors. Semin Urol 1988; 6: 171–88.

96. Williams SD, Einhorn LH. Neoplasms of the testis. In: Calabresi P, Schein PS, Rosenberg SA, eds: Medical Oncology: Basic Principles and Clinical Management of Cancer. New York: Macmillan, 1985; 1077–88.

97. Teilum G, Endodermal sinus tumor of the ovary and testis. Cancer 1959; 12: 1092–105.

98. Brosman SA. Testicular tumors in prepubertal children. Urology 1979; 13: 581–8.

99. Niehans GA, Manivel JC, Copland GT et al. Immunohistochemistry of germ cell and trophoblastic neoplasms. Cancer 1988; 62: 1113–23.

100. Perlman EJ, Cushing B, Hawkins E et al. Cytogenetic analysis of childhood endodermal sinus tumor: a Pediatric Oncology Group study. Pediatr Pathol 1994; 14: 695–708.

101. Kaplan GW, Cromie WC, Kelealis PP et al. Prepubertal yolk sac testicular tumors–report of the testicular tumor registry. J Urol 1988; 140: 1109–12.

102. Kaplan WE, Firlit CF. Treatment of testicular yolk sac carcinoma in the young child. J Urol 1981: 126: 663–4.

103. Ross JH, Rybicki L, Kay R, Clinical behaviour and a contemporary management algorithm for prepubertal testis tumors: a summary of the prepubertal testis tumor registry. J Urol 2002; 168: 1675–8.

104. Ulbright TM, Young RH, Scully RE. Trophoblastic tumors of the testis other than classic choriocarcinoma: 'monophasic' choriocarcinoma and placental site trophoblastic tumor: a report of two cases. Am J Surg Pathol 1997; 21: 282–8.

105. Suurmeijer AJ, Gietema JA, Hoekstra HJ. Placental site trophoblastic tumor in a late recurrence of a nonseminomatous germ cell tumor of the testis. Am J Surg Pathol 2004; 28: 830–3.

106. Petignat P, Billieux MH, Blouin JL et al. Is genetic analysis useful in the routine management of hydatidiform mole? Hum Reprod 2003; 18: 243–9.

107. van Echten J, van Doorn LC, van der Linden HC et al. Cytogenetics of a malignant ovarian germ-cell tumor. Int J Cancer 1998; 77: 217–18.

108. Giralt SA, Dexeus F, Amato R et al. Hyperthyroidism in men with germ cell tumors and high levels of beta-human chorionic gonadotropin. Cancer 1992; 69: 1286–90.

109. Bower M, Newlands E, Holden L et al. Treatment of men with metastatic non-seminomatous germ cell tumors with cyclical POMB/ACE chemotherapy. Ann Oncol 1997; 8: 477–83.

110. Logothetis CJ, Samuels ML, Selig DE et al. Cyclic chemotherapy with cyclophosphamide, doxorubicin, and cisplatin plus vinblastine and bleomycin in advanced germinal tumors. Am J Med 1986; 81: 219–28.

111. Virchow R. Die krankhaften Geschwülste. Verlag A. Berlin, Hirschwald: 1863.

112. Pichmann S, Mikuz G, Schmid KW. Chromogranins A and B in non-seminomatous testicular tumors. J Uropathol 1993; 1: 43–54.

113. Damjanov I. Tumors of the testis and epididymis. In: Murphy WM, ed. Urological Pathology, 2nd edn. Philadelphia, (WB Saunders Company London, Toronto, Montreal, Sydney, Tokyo) 277–341.

114. Garett JE, Cartwright PC, Snow BW et al. Cystic testicular lesions in the pediatric population. J Urol 2000; 163: 928–36.

115. Ulbright TM, Srigley JR. Dermoid cyst of the testis: a study of five post-pubertal cases, including a pilomatrixoma-like variant, with evidence supporting its separate classification from mature testicular teratoma. Am J Surg Pathol 2000; 25: 788–93.

116. Shah KH et al. Epidermoid cyst of the testis: a report of three cases and analysis of 141 cases from the world literature: Cancer 1981; 47: 577–82.

117. Heidenreich A, Zumbe J, Vorreuther R et al. Testikuläre Epidermiszyste: Orchiektomie oder Enukleationsresektion? Urologe A 1996; 35: 1–5.

118. Zavala-Pompa A, Ro JY, El-Naggar A et al. Primary carcinoid tumor of the testis. Immunohistochemical, ultrastructural, and DNA flow cytometric study of three cases with a review of the literature. Cancer 1993; 72: 1726–32.

119. Ulbright TM, Loehrer PJ, Roth LM et al. The development of non-germ cell malignancies within germ cell tumors. A clinicopathologic study of 11 cases. Cancer 1984; 54: 1824–33.

120. Comiter CV, Kibel AS, Richie JP et al. Prognostic features of teratomas with malignant transformation: a clinicopathological study of 21 cases. J Urol 1998; 859–63.

121. Molenaar WM, Oosterhuis JW, Meiring A et al. Histology and DNA contents of a secondary malignancy arising in a mature residual lesion six years after chemotherapy for a disseminated nonseminomatous testicular tumor. Cancer 1986; 58: 264–8.

122. Motzer RJ, Amsterdam A, Prieto V et al. Teratoma with malignant transformation: diverse malignant histologies arising in men with germ cell tumors. J Urol. 1998; 159: 133–8.

123. Grady RW, Ross JH, Kay R. Epidemiological features of testicular teratoma in a prepubertal population. J Urol 1997; 158: 1191–2.

124. Mosharafa AA, Foster RS, Leibovich BC et al. Histology in mixed germ cell tumors. Is there a favourite pairing? J Urol 2004; 171: 1471–3.

125. Freedman LS, Parkinson MC, Jones WG et al. Histopathology in the prediction of relapse of patients with stage I testicular teratoma treated by orchidectomy alone. Lancet 1987; 2: 294–8.

126. Albers P, deRiese W, Walker EB et al. Predictive parameters in biologic assessment of low-stage retroperitoneal lymph-node dissection. World J Urol 1994; 12: 120–4.

127. Ulbright TM, Orazi A, de Riese W et al. The correlation of P53 protein expression with proliferative activity and occult metastases in clinical stage I non-seminomatous germ cell tumors of the testis. Mod Pathol 1994; 7: 64–8.

128. Hildenbrand G, Weißbach L, Oberhoffer G et al. In: Weißbach L, Hildenbrand G, eds. Register und Verbundstudie für Hodentumoren–Bonn. Ergebnisse einer prospektiven Untersuchung. München: W Zuckschwerdt Verlag, 1982; 125–36.

129. Donohue JP. Metastatic pathways of non seminomatous germ cell tumors. Semin Urol 1984; 2: 217–29.

130. Sheinfeld J, Motzer RJ, Rabbani F et al. Incidence and clinical outcome of patients with teratoma in the retroperitoneum following primary retroperitoneal lymph node dissection for clinical stages I and IIA non-seminomatous germ cell tumors. J Urol 2003; 170: 1159–62.

131. Carver BS, Bianco FJ, Shayegan B et al. Predicting teratoma in the retroperitoneum in men undergoing post chemotherapy retroperitoneal lymph node dissection. J Urol 2006; 176: 100–4.

132. Michael H, Lucia J, Foster RS et al. The pathology of late recurrence of testicular germ cell tumors. Am J Surg Pathol 2000; 24: 257–73.

133. Rustin GJ, Vogelzang NJ, Sleijfer DT et al. Consensus statement on circulating tumor markers and staging patients with germ cell tumors. Prog Clin Biol Res 1990; 357: 277–84.

134. Scholz M, Zehender M, Thalmann GN et al. Extragonadal retroperitoneal germ cell tumor: evidence of origin in the testis. Ann Oncol 2002; 13: 121–4.

135. Bär W, Hedinger Chr. Ausgebrannte (okulte) Hodentumoren. Hodenläsionen bei klinisch scheinbar primär extratestikulären malignen Keimzelltumoren. Virch Arch A Path Anat Histol 1977; 377: 67–87.

136. Lopez JI, Angulo JC. Burned out tumor of the testis presenting as retroperitoneal choriocarcinoma. Int Urol Nephrol 1994; 26: 549–53.

137. Casella R, Rochlitz C, Sauter G et al. Der 'ausgebrante' Hodentumor: eine seltene Erscheinungsform der Keimzellneoplasien. Schweiz Med Wochenschr 1999; 129: 235–40.

138. Ulbright TM, Amin MB, Young RH. Tumors of the Testis, Adnexa, Spermatic Cord, and Scrotum. AFIP Atlas of Tumor Pathology, 3rd series, Fascicle 25. Washington DC, Armed Forces Institute of Pathology 1999; 193–233.

139. Algaba F, Arce Y, Lopez-Beltran A et al. European Society of Uropathology; Uropathology Working Group. Intraoperative frozen section diagnosis in urological oncology. Eur Urol. 2005; 47: 129–36.

140. Teilum G. Special Tumors of the Ovary, and Testis, 2nd edn. Munksgard, Copenhagen; 1976.

141. Kim I, Young RH, Scully RE. Leydig cell tumors of the testis. A clinicopathological analysis of 40 cases and review of the literature. Am J Surg Pathol 1985; 9: 177–92.

142. Ulbright TM, Srigley JR, Hatzianastassiou DK et al. Leydig cell tumors of the testis with unusual features: adipose differentiation, calcification with ossification, and spindle-shaped tumor cells. Am J Surg Pathol 2002; 26: 1424–33.

143. Lawrence WD, Young RH, Scully RE. Sex cord–stromal tumors. In: Talerman A, Roth LM eds. Pathology of the Testis and its Adnexa. New York, Edinburgh, London, Melbourne, Churchill Livingstone, 1986; 67–92.

144. Busam KJ, Iversen K, Coplan KA et al. Immunoreactivity for A103, an antibody to melan-A (Mart-1), in adrenocortical and other steroid tumors. Am J Surg Pathol 1998; 22: 57–63.

145. Kommoss F, Oliva E, Bittinger F et al. Inhibin-alpha CD99, HEA125, PLAP, and chromogranin immunoreactivity in testicular neoplasms and the androgen insensitivity syndrome. Hum Pathol. 2000; 31: 1055–61.

146. Mikuz G, Damjanov I. Inflammation of the testis, epididymis, peritesticular membranes, and scrotum. Pathol Annu 1982; 17: 101–28.

147. Okada H, Gotoh A, Takechi Y et al. Leydig cell tumor of the testis associated with Klinefelter's syndrome and Osgood–Schlatter disease. Br J Urol 1994; 73: 457.

148. Rutgers JL, Scully RE. Pathology of the testis in intersex syndromes. Semin Diagn Pathol 1987; 4: 275–91.

149. Mikuz G, Loewit K, Herbst M. Über nebennierenrindenartige Leydig'sche Zwischenzellen. Virch Arch Abt B [Zellpath] 1975; 19: 359–68.

150. Cheville JC, Sebo TJ, Lager DJ et al. Leydig cell tumor of the testis: a clinicopathologic, DNA content and MIB-1 comparison of non-metastasizing and metastasizing tumors. Am J Surg Pathol 1998; 22: 1361–7.

151. Grem JL, Robins HI, Wilson KS et al. Metastatic Leydig cell tumor of the testis. Report of three cases and review of the literature Cancer. 1986; 58: 2116–19.

152. Verdorfer I, Horst D, Höllrigl A et al. Leydig cell tumors of the testis. A molecular cytogenetic study based on a series of 25 patients. Oncol Rep 2007; 17: 585–9.

153. Bercovici JP, Nahoul K, Tater D et al. Hormonal profile of Leydig cell tumors with gynecomastia. J Clin Endocrinol Metab. 1984; 59: 625–63.

154. Bercovici JP, Nahoul K, Ducasse M et al. Leydig cell tumor with gynecomastia: further studies–the recovery after unilateral orchidectomy. J Clin Endocrinol Metab. 1985; 61: 957–62.

155. Konrad D, Schoenle EJ. Ten-year follow-up in a boy with Leydig cell tumor after selective surgery. Horm Res. 1999; 51: 96–100.

156. Shukla AR, Woodard C, Carr MC et al. Experience with testis sparing surgery for testicular teratoma. J Urol 2004; 171: 161–3.

157. Mosharafa AA, Bertram KA, Bratloff B et al. Treatment of malignant Leydig cell tumor. Cancer 1991; 68: 2324–9.

158. Bertram KA, Bratloff B, Hodges GF et al. Treatment of malignant Leydig cell tumor. Cancer 1991; 68: 2324–9.

159. Young RH, Koelliker DD, Scully RE. Sertoli cell tumors of the testis, not otherwise specified: a clinicopathologic analysis of 60 cases. Am J Surg Pathol 1998; 22: 709–21.

160. Young S, Gooneratne S, Straus FH et al. Feminizing Sertoli cell tumors in boys with Peutz–Jeghers syndrome. Am J Surg Pathol 1995; 19: 50–8.

161. Carney JA, Gordon H, Carpenter PC et al. The complex of myxomas, spotty pigmentation, and endocrine overactivity. Medicine (Baltimore) 1985; 64: 270–83.

162. Madsen EL, Hultberg BM. Metastasizing Sertoli cell tumors of the human testis–a report of two cases and review of the literature. Acta Oncol 1990; 29: 946–9.

163. Henley JD, Young RH, Ulbright TM. Malignant Sertoli cell tumors of the testis: a study of 13 examples of a neoplasm frequently misinterpreted as seminoma. Am J Surg Pathol 2002; 26: 541–50.

164. Zuckerberg LR, Young RH, Scully RE. Sclerosing Sertoli cell tumor of the testis: a report of 10 cases. Am J Surg Pathol 1991; 15: 829–64.

165. Hedinger CE, Plattner D. Dysgenetische, sogenannte hypoplastische Zonen in retiniertenund beidseits normal deszendierten Hoden. Pathol Microbiol 1961; 24: 227–33.

166. Jacobsen GK. Malignant Sertoli cell tumors of the testis. J Urol Pathol 1993; 1: 233–55.

167. Talerman A. Malignant Sertoli cell tumor of the testis. Cancer 1971; 28: 446–55.

168. Verdorfer I, Höllrigl A, Strasser U et al. Molecular-cytogenetic characterisation of sex cord-stromal tumors: CGH analysis in Sertoli cell tumors of the testis. Virch Arch 2007; 450: 425–31.

169. Alikasifoglu A, Gonc EN, Akcoren Z et al. Feminizing Sertoli cell tumor associated with Peutz–Jeghers syndrome. J Pediatr Endocrinol Metab 2002; 15: 449–52.

170. Demir A, Önol FF, Türkeri L. Case report: malignant Sertoli cell tumor of the testis in adult. Int Urol Nephrol 2004; 35: 515–16.

171. Proppe KH, Scully RE. Large cell calcifying Sertoli cell tumor of the testis. Am J Clin Pathol 1980; 74: 607–19.

172. Kratzer SS, Ulbright TM, Talerman A et al. Large cell calcifying Sertoli cell tumor of the testis: contrasting features of six malignant and six benign tumors and a review of the literature. Am J Surg Pathol 1997; 21: 1271–80.

173. Bufo P, Pennella A, Serio G et al. Malignant large cell calcifying Sertoli cell tumor of the testis (LCCSCTT). Report of a case in an elderly man and review of the literature. Pathologica 1999; 91: 107–14.

174. Proppe KH, Dickersin GR. Large-cell calcifying Sertoli cell tumor of the testis: light microscopic and ultrastructural study. Hum Pathol 1982; 13: 1109–14.

175. Suppiah A, Musa MM, Morgan DR et al. Adult granulosa cell tumor of the testis and bony metastasis. A report of the first case of granulosa cell tumor of the testicle metastasising to bone. Urol Int. 2005; 75: 91–3.

176. Young RH, Lawrence WD, Scully RE. Juvenile granulosa cell tumor–another neoplasm associated with abnormal chromosomes and ambiguous genitalia. A report of three cases. Am J Surg Patho 1985; 19: 737–43.

177. Tanaka Y, Sasaki Y, Tachibana K et al. Testicular juvenile granulosa cell tumor in an infant with X/XY mosaicism clinically diagnosed as true hermaphroditism. Am J Surg Pathol 1994; 18: 316–22.

178. Harms D, Kock LR. Testicular juvenile granulosa cell and Sertoli cell tumors: a clinicopathological study of 29 cases from the Kiel Paediatric Tumor Registry. Virch Arch 1997; 430: 301–9.

179. Deveci MS, Deveci G, Onguru O et al. Testicular gonadal stromal fibroma: case report and review of the literature. Pathol Int 2002; 52: 326–30.

180. Renshaw AA, Gordon M, Corless CL. Immunohistochemistry of unclassified sex cord–stromal tumors of the testis with a predominance of spindle cells. Mod Pathol 1997; 10: 693–700.

181. Ulbright TM, Young RH. Primary mucinous tumors of the testis and paratestis: a report of nine cases. Am J Surg Pathol 2003; 27(9): 1221–8.

182. Scully RE. Gonadoblastoma. A gonadal tumor related to the dysgerminoma (seminoma) and capable of sex hormone production. Cancer 1953; 6: 445–63.

183. Talerman A. A distinctive gonadal neoplasm related to gonadoblastoma. Cancer 1972; 30: 1219–24.

184. Ulbright TM, Srigley JR, Reuter VE et al. Sex cord–stromal tumors of the testis with entrapped germ cells: a lesion mimicking unclassified mixed germ cell sex cord-stromal tumors. Am J Surg Pathol 2000; 24: 535–42.

185. Michal M, Vanecek T, Sima R et al. Mixed germ cell sex cord-stromal tumors of the testis and ovary. Morphological, immunohistochemical, and molecular genetic study of seven cases. Virch Arch. 2006; 448: 612–22.

186. Masson P. Pflügerome. Bull Soc Anat Paris 1912; 14: 403–4.

187. Scully RE, Gonadoblastoma. A review of 74 cases. Cancer 1970; 25: 1340–56.

188. Pohl HG, Shukla AR, Metcalf PD et al. Prepubertal testis tumors: actual prevalence rate of histological types. J Urol 2004; 172: 2370–2.

189. Cools M, Drop SL, Wolffenbuttel KP et al. Germ cell tumors in the intersex gonad: old paths, new directions, moving frontiers. Endocr Rev 2006; 27: 468–84.

190. McTaggart SJ, Algar E, Chow CW et al. Clinical spectrum of Denys–Drash and Frasier syndrome. Pediatr Nephrol 2001; 16: 335–9.

191. Saylam K, Simon P. WT1 gene mutation responsible for male sex reversal and renal failure: the frasier syndrome. Eur J Obstet Gynecol Reprod Biol 2003; 110: 111–13.

192. Kato N, Motoyama T, Kameda N et al. Primary carcinoid tumor of the testis: immunohistochemical, ultrastructural and FISH analysis with review of the literature. Pathol Int 2003; 53: 680–5.

193. Amin MB. Selected other problematic testicular and paratesticular lesions: rete testis neoplasms and pseudotumors, mesothelial lesions and secondary tumors. Mod Pathol 2005; 18 (Suppl 2): S131–45.

194. Young RH, Scully RE. Testicular and paratesticular tumors and tumor-like lesions of ovarian common epithelial and Müllerian types. Am J Clin Pathol 1986; 86: 146–52.

195. Jones MA, Young RH, Srigley JR et al. Paratesticular serous papillary carcinoma. A report of six cases. Am J Surg Pathol 1995; 19: 1359–65.

196. Ulbright TM, Young RH. Primary mucinous tumors of the testis and paratestis: a report of nine cases. Am J Surg Pathol 2003; 27: 1221–8.

197. Henley JD, Ferry J. Ulbright TM. Miscellaneous rare paratesticular tumors. Semin Diagn Pathol 2000; 17: 319–39.

198. Zucca E, Conconi A, Mughal TI et al. Patterns of outcome and prognostic factors in primary large-cell lymphoma of the testis in a survey by the International Extranodal Lymphoma Study Group. J Clin Oncol 2003; 21: 20–7.

199. Anghel G, Petti N, Remotti D et al. Testicular plasmacytoma: report of a case and review of the literature. Am J Hematol 2002; 71: 98–104.

200. Ferry JA, Harris NL, Young RH et al. Malignant lymphoma of the testis, epididymis, and spermatic cord. A clinicopathologic study of 69 cases with immunophenotypic analysis. Am J Surg Pathol 1994; 18: 376–90.

201. Darby S, Hancock BW. Localised non-Hodgkin lymphoma of the testis: the Sheffield Lymphoma Group experience. Int J Oncol 2005; 26: 1093–9.

202. Moller MB, d'Amore F, Christensen BE. Testicular lymphoma: a population-based study of incidence clinicopathological correlations and prognosis. The Danish Lymphoma Study Group, LYFO. Eur J Cancer 1994; 30A: 1760–4.

203. Kim YB, Chang SK, Yang WI et al. Primary NK/T cell lymphoma of the testis. A case report and review of the literature. Acta Haematol. 2003; 109: 95–100.

204. Givler RL. Testicular involvement in leukaemia and lymphoma. Cancer 1969; 23: 1290–5.

205. Miller DR, Leikin Sl, Albo VC et al. The prognostic value of testicular biopsy in childhood acute lymphoblastic leukemia: a report from the Childrens Cancer Study Group. J Clin Oncol 1990; 8: 57–66.

206. McIlwain L, Sokol L, Moscinski LC et al. Acute myeloid leukemia mimicking primary testicular neoplasm. Presentation of a case with review of literature. Eur J Haematol 2003; 70: 242–5.

207. Jones EC, Murray SK, Young RH. Cysts and epithelial proliferations of the testicular collecting system (including rete testis). Semin Diagn Pathol 2000; 17: 270–93.

208. Jones MA, Young RH, Srigley JR et al. Paratesticular serous papillary carcinoma. A report of six cases. Am J Surg Pathol 1995; 19: 1359–65.

209. Nochomovitz LE, Orenstein JM. Adenocarcinoma of the rete testis. Consolidation and analysis of 31 reported cases with a review of miscellaneous entities. J Urol Pathol 1994; 2: 1–37.

210. Pozza D, Masci P, Amodeo S et al. Papillary cystadenoma of the epididymis as a cause of obstructive azoospermia. Urol Int 1994; 53: 222–4.

211. Patel SR, Richardson RL, Kvols L. Metastatic cancer to the testes: a report of 20 cases and review of the literature. J Urol L 1989; 142: 1003–5.

212. Pienkos JE, Jablokow VR. Secondary testicular tumors. Cancer 1972; 30: 481–5.

213. Haupt HM, Mann RB, Trump DL et al. Metastatic carcinoma involving the testis. Clinical and pathologic distinction from primary testicular neoplasms. Cancer 1984; 54: 709–14.

214. Johansson JE, Lannes P. Metastases to the spermatic cord, epididymis and testicles from carcinoma of the prostate–five cases. Scand J Urol Nephrol 1983; 17: 249–51.

215. Jones MA, Young RH, Scully RE et al. Benign fibromatous tumors of the testis and paratesticular region: a report of 9 cases with a proposed classification of fibromatous tumors and tumor-like lesions. Am J Surg Pathol. 1997; 21: 296–305.

216. Banks ER, Mills SE. Histiocytoid (epithelioid) hemangioma of the testis. The so-called vascular variant of 'adenomatoid tumor'. Am J Surg Pathol 1990; 14: 584–9.

217. Washecka RM, Mariani AJ, Zuna RE et al. Primary intratesticular sarcoma. Immunohistochemical ultrastructural and DNA flow cytometric study of three cases with a review of the literature. Cancer 1996; 77: 1524–8.

218. Lee JS, Choi YD, Choi C. Primary testicular osteosarcoma with hydrocele. Virch Arch. 2004; 445: 210–13.

219. Mašera A, Ovčak Z, Mikuz G. Angiosarcoma of the testis. Virch Arch 1999; 434: 351–3.

220. Lee KC, Yeung K, Welsh C et al. Angiosarcoma following treatment of testicular seminoma: case report and literature review. J Urol 1995; 153: 1055–6.

221. Shih DF, Wang JS, Tseng HH et al. Primary squamous cell carcinoma of the testis. J Urol 1996; 156: 1772.

222. Wernert N, Goebbels R, Prediger L. Papillary cystadenoma of the epididymis. Case report and review of the literature. Pathol Res Pract 1986; 181: 260–4.

223. Gilcrease MZ, Schmidt L, Zbar B et al. Somatic von Hippel Lindau mutation in clear cell papillary cystadenoma of the epididymis. Hum Pathol 1995; 26: 1341–6.

224. Ganem JP, Jhaveri FM, Marroum MC. Primary adenocarcinoma of the epididymis: case report and review of the literature. Urology 1998; 52: 904–8.

225. Williams SB, Han M, Jones R et al. Adenomatoid tumor of the testes. Urology 2004; 63: 779–81.

226. Woodward PJ, Schwab CM, Sesterhenn IA. From the archives of the AFIP: extratesticular scrotal masses: radiologic–pathologic correlation. Radiographics 2003; 23: 215–40.

227. Janssen-Heijen ML, Damhuis RA, Klinkhamer PJ et al. Increased but low incidence and poor survival of malignant mesothelioma in the south eastern part of the Netherlands since 1970: a population-based study. Eur J Cancer Prev 1999; 8: 311–14.

228. Murai Y. Malignant mesothelioma in Japan: analysis of registered autopsy cases. Arch Environ Health 2001; 56: 84–8.

229. Plas E, Riedl CR, Pfluger H. Malignant mesothelioma of the tunica vaginalis testis. Cancer 1998; 83: 2437–46.

230. Huncharek M. Genetic factors in the aetiology of malignant mesothelioma. Eur J Cancer 1995; 31: 1741–7.

231. Eimoto T, Inoue I. Malignant fibrous mesothelioma of the tunica vaginalis. Cancer 1977; 39: 2059–66.

232. Mikuz G, Hopfel-Kreiner I. Papillary mesothelioma of the tunica vaginalis propria testis. Case report and ultrastructural study. Virch Arch A Pathol Anat Histol 1982; 396: 231–8.

233. Lane TM, Wilde M, Schofield J et al. Benign cystic mesothelioma of the tunica vaginalis. BJU Int 1999; 84: 533–4.

234. Churg A. Paratesticular mesothelial proliferations. Semin Diagn Pathol 2003; 20: 272–8.

235. Krismann M, Muller KM, Jaworska M et al. Molecular cytogenetic differences between histological subtypes of malignant mesotheliomas: DNA cytometry and comparative genomic hybridization of 90 cases. J Pathol 2002; 197: 363–71.

236. Gupta NP, Kumar R. Malignant gonadal mesothelioma. Curr Treat Options Oncol 2002; 3: 363–7.

237. Kruse-Losler B, Gaertner C, Burger H et al. Melanotic neuroectodermal tumor of infancy: systematic review of the literature and presentation of a case. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006; 102: 204–16.

238. Anagnostaki L, Krag Jacobsen G, Horn T et al. Melanotic neuroectodermal tumour as a predominant component of an immature testicular teratoma. Case report with immunohistochemical investigations. APMIS 1992; 100: 809–16.

239. Cummings OW, Ulbright TM, Young RH et al. Desmoplastic small round cell tumors of the paratesticular region. A report of six cases. Am J Surg Patholean 1997; 21: 219–25.

240. Weiss SW, Goldblum GR. Enzinger and Weiss's Soft Tissue Tumors, 4th edn. St. Louis, London, Philadelphia, Sydney, Toronto, Mosby 2001; 785–835.

241. Idrees MT, Hoch BL, Wang BY et al. Aggressive angiomyxoma of male genital region. Report of 4 cases with immunohistochemical evaluation including hormone receptor status. Ann Diagn Pathol. 2006; 10: 197–204.

242. Dahl V, Bahn RC. Aberrant adrenal cortical tissue near the testis in human infants. Am J Pathol. 1962; 40: 587–98.

243. Nistal M, Regadera J, Paniagua R et al. Cystic dysplasia of the testis. Light and electron microscopic study of three cases. Arch Pathol Lab Med. 1984; 108: 579–83.

244. Gondos B, Egli CA, Rosenthal SM et al. Testicular changes in gonadotropin-independent familial male sexual precocity. Familial testotoxicosis. Arch Pathol Lab Med 1985; 109: 990–5.

245. Mikuz G. Elektronenmikroskopische Untersuchung an zwei Fällen granulomatöser Orchitis. Virch Arch A Path Anat 1973; 360: 223–34.

246. McClure J. Malakoplakia of the testis and its relationship to granulomatous orchitis. J Clin Pathol. 1980; 33: 670–8.

247. Jones MA, Young RH, Scully RE et al. Benign fibromatous tumors of the testis and paratesticular region: a report of 9 cases with a proposed classification of fibromatous tumors and tumor-like lesions. Am J Surg Pathol 1997; 21: 296–305.

248. Seethala RR, Tirkes AT, Weinstein S et al. Diffuse fibrous pseudotumor of the testicular tunics associated with an inflamed hydrocele. Arch Pathol Lab Med. 2003; 127: 742–4.

249. Oertel YC, Johnson FB. Sclerosing lipogranuloma of male genitalia. Review of 23 cases. Arch Pathol Lab Med 1977; 101: 321–6.

250. Matsuda T, Shichiri Y, Hida S et al. Eosinophilic sclerosing lipogranuloma of the male genitalia not caused by exogenous lipids. J Urol 1988; 140: 1021–4.

251. Lowenthal SB, Goldstein AM, Terry R et al. Cholesterol granuloma of tunica vaginalis simulating testicular tumor. Urology 1981; 18: 89–90.

252. Mikuz G, Hofstadter F, Hager J et al. Testis involvement in Schonlein–Henoch purpura. Pathol Res Pract. 1979; 165: 323–9.

253. McDonald SW. Cellular responses to vasectomy. Int Rev Cytol 2000; 199: 295–339.

254. Oliva E, Young RH. Paratesticular tumor-like lesions. Semin Diagn Pathol 2000; 17: 340–58.

255. Shned AR, Selikowitz SM. Epididymitis nodosa. An epididymal lesion analogous to vasitis nodosa. Arch Pathol Lab Med. 1986; 110: 61–4.

256. Duncan WL Jr, Barraza MA. Splenogonadal fusion: a case report and review of literature. J Pediatr Surg 2005; 40: E5–E7.

257. Ferro F, Lais A, Boldrini R et al. Hepatogonadal fusion. J Pediatr Surg 1996; 31: 435–6.

258. Woodhouse JB, Delahunt B, English SF et al. Testicular lipomatosis in Cowden's syndrome. Mod Pathol. 2005; 18: 1151–6.

259. Winstanley AM, Mikuz G, Debruyne F et al. Handling and reporting of biopsy and surgical specimens of testicular cancer. Eur Urol 2004; 564–73.

Section 7

Squamous cell carcinoma of the penis

Antonio L Cubilla and Elsa F Velazquez

Definition

The mucosal surface of the penis extends from the preputial orifice to the urethral meatus and comprises the three penile epithelial compartments: foreskin inner surface, coronal sulcus, and glans.[1,2] The vast majority of penile cancers are squamous cell carcinoma (SCC) arising in the squamous epithelium of one of these anatomic compartments.[1,2] Primary cancers of the outer penile skin are extremely rare. We have identified only three cases after the examination of more than 1000 penectomy specimens with cancer. Distal urethral tumors are also unusual and in general discussed with urothelial cancers. Penile sarcomas and lymphomas are exceptional.[2]

Epidemiology and etiology

Penile cancer is comparatively a rare disease with incidence rates in the Western world in the range of 0.3–1.0/100 000, but there is great variation among different countries.[3] The incidence of penile SCC varies from a high incidence in Uganda, Kenya, some regions of tropical or subtropical South America, Circumpolar Inuit, and Asia to a lower incidence in Northern Europe and the United States, Japan north to Okinawa and Israel.[4–7] A decreasing incidence of penile cancer has been noted in several studies,[8,9] but a recent increase has been reported in some regions of Spain.[10] The high frequency of penile cancer has not changed in the rural population of Paraguay in the last 50 years.

Comparing cases from the United States and Paraguay, we found no geographic differences in the morphology and relative incidence of histologic subtypes.[11] Differences in geographic distribution of penile cancers are attributed to environmental factors.[12] Several epidemiologic studies indicate the following risk factors: socioeconomic deprivation, poor hygiene habits, lack of access to running water, phimosis, smegma retention, lack of circumcision, chronic inflammation, history of tear or injury to the penis, physical inactivity, history of warts, ultraviolet irradiation, partner with cervical cancer, immunosuppression, smoking, HPV and lichen sclerosus.[13–17] Early circumcision appears to be associated with a lower incidence of penile cancer when compared to later circumcision. Penile carcinoma in circumcised men is very rare; however, it has been reported in association with irregular scarring in patients undergoing ritual vigorous circumcision. These post-circumcision penile SCCs appear to be biologically aggressive.[18] Socioeconomic differences among patients with penile cancers were found to be small and not significant in a Finnish study.[19]

There is a coexisting high incidence of penile and cervical cancers in some areas of the world.[20] However, pathologically penile cancers are more similar to vulvar cancers.[21] The overall prevalence of HPV DNA in penile carcinoma (42%) is lower than in cervical carcinoma (near 100%) and similar to vulvar carcinomas (approximately 50%). Specific histologic subtypes of penile cancer, basaloid and warty, are consistently associated with HPV whereas the viral presence is unusual in the usual (common) type of SCC as well as in verrucous, papillary, and sarcomatoid carcinomas.[22,23] These two groups of tumors appear to develop along different pathogenetic pathways. HPV 16 is the most common type of HPV associated with penile cancer. There is, however, one Argentinian study in which the subtype 18 was found to be the most prevalent.[24] The prevalence of HPV DNA in male partners of HPV-infected women is high (76%), but pathologic HPV-associated lesions are unusual (13.5%). HPV DNA is more frequently found in partners of women with cervical intra-epithelial lesion (CIN) than in sporadic cases (59 vs 25%).[25] HPV-related tumors are known to occur in HIV-infected patients.[26,27] A prospective study revealed that HPV-related anogenital cancers (in situ and invasive), including penile cancers, were significantly more frequent in HIV-infected patients compared with the expected number of cancers in the general population.[27] A recent report from Brazil found Epstein-Barr virus (EBV) DNA in 20 of 21 penile tumor samples, independently of histologic type.[28]

Clinical features

Overall, penile cancer affects males in the sixth decade (mean age is 60 years). HPV-related tumors such as warty and basaloid cancers affect younger patients (45–55 years) and verrucous and pseudohyperplastic carcinomas occur at an older age (70–80 years).[29] A recent study from Nairobi showed a relatively young peak age of 47.9 years for all penile cancers at the Kenyatta National Hospital.[30]

Patients with penile cancer usually consult with an exophytic mass (Figure 7.1) or a flat ulcerated lesion (Figure 7.2). In our experience with rural Paraguayan patients, about 40% present with inguinal lymph node metastasis and 10% with disseminated disease. This high figure contrasts with a significantly lower incidence of regional and systemic metastasis in North American patients (13 and 2.3%, respectively).[31] In some patients, the primary tumors may be subtle and characterized by an irregular erythematous lesion in the glans. In phimotic patients, the primary tumor may be concealed by the phimotic prepuce and regional metastases may be the presenting sign (Figure 7.3). In a prospective evaluation of 23 consecutive patients with penile cancer, we found long foreskins in 77% of

Figure 7.1
Large exophytic mass extensively affecting the distal part of the penis.

Figure 7.2
Some lesions are flat and ulcerated. However, on cut sections, flat lesions may be deeply invasive lesions.

the patients, 52% of which also had phimosis. In a control group including men from the general population from the same socioeconomic background, long foreskins were present at a similar rate of 77%, but phimosis was present in only 7%.[32]

The fact that the majority of our cases present as unicentric tumors (90–95%)[33] may reflect the rather advanced clinical stage of our patients. Carcinomas affecting exclusively the foreskin are more frequently multicentric and this finding may be related to the frequent association of these tumors with lichen sclerosus.[34]

The frequency of in situ and invasive carcinomas also varies according to geographic regions. In areas where penile cancer is considered endemic or epidemic, and most likely due to diagnostic delay,

Figure 7.3
Patient with phimosis in which the primary tumor was concealed by the phimotic prepuce. Regional metastases were the presenting sign on this case.

most tumors present as invasive lesions, whereas in regions where penile cancer is unusual, carcinoma in situ is relatively more frequent. In a series of 500 invasive carcinomas diagnosed in Paraguay, we found only 20 cases of carcinoma in situ (4%), whereas of 1605 cases from the SEER database in the USA the figure was 37%,[31] and this figure appears to be increasing. It may be that geographic differences in fact reflect mostly the incidence of invasive cancers and that if all precancerous and invasive lesions were taken into account the difference would diminish or vanish.

Morphologic features

Squamous cell carcinoma of the usual type (synonyms: SCC NOS, typical, common, simplex)

Squamous cell carcinoma of the usual type is morphologically similar to SCCs of other sites and accounts for 55% of all penile carcinomas. In a prior anatomic study, we found three different patterns of growth (excluding verruciforms): superficial spreading, multicentric, and vertical growth.[33] Superficially spreading lesions are composed of an extensive intra-epithelial component (horizontal growth), usually associated with a superficially invasive cancer (Figure 7.4). It frequently affects the three epithelial compartments, foreskin, coronal sulcus and glans, and the incidence of metastasis is low. Due to the subclinical spread of these tumors and subsequent insufficient surgery, recurrences may occur. The same is true for multicentric SCCs, which account for about 5–10% of all penile cancers (Figure 7.5). They are usually low-grade lesions with good prognosis. Tumors with a vertical pattern of growth are deeply invasive and associated with a high rate of nodal regional metastasis (Figure 7.6).

Grossly, SCCs of the usual type vary from irregular, white-gray exophytic to flat ulcerated endophytic masses. The cut surface shows irregular, white-gray neoplastic tissues involving lamina propria, corpus spongiosum or corpus cavernosum in the glans and dartos or skin in the foreskin. The boundaries between tumor and stroma are

A

B
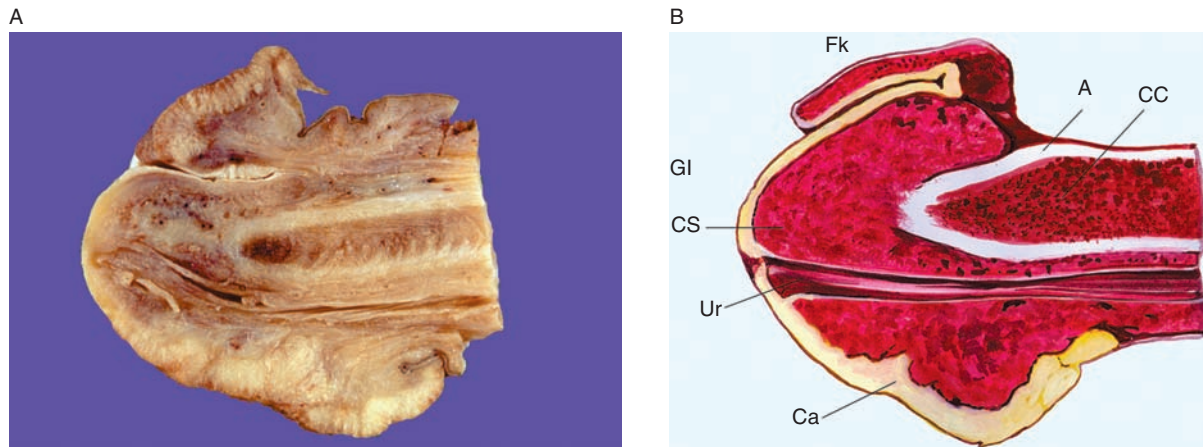
Figure 7.4
(A) and (B) Gross picture and diagram illustrating the cut section of a superficially spreading carcinoma composed of an extensive intra-epithelial component (horizontal growth), associated with a superficially invasive cancer. Gl: glans, Fk: foreskin, CS: corpus spongiosum, CC: corpus cavernosum, A: albuginea, Ur: urethra, Ca: carcinoma.

Figure 7.5
Multicentric preputial carcinoma. The smaller tumor corresponded to a well-differentiated SCC and the larger one was a sarcomatoid carcinoma.

usually jagged and irregular but in some cases a sharper delineation may be noted. On cut surface, adjacent associated epithelial lesions such as squamous hyperplasia or low- and high-grade squamous intraepithelial lesions can be visualized as a marble line measuring 1–2 mm in thickness in the adjacent epithelium (Figure 7.4). Microscopically, the neoplasms vary from well-differentiated keratinizing (Figure 7.7) to solid anaplastic carcinomas with scant or no keratinization (Figure 7.8). Most tumors are highly keratinized and of moderate differentiation (Figure 7.9). Poorly differentiated carcinomas may have variable amounts of spindle cell, giant cell, solid, acantholytic, clear cell, small cell, basaloid, or glandular components.

Basaloid carcinomas

Basaloid carcinoma is an aggressive, HPV-related variant of SCC occurring in the 5th decade and preferentially affecting the glans. It accounts for 5–10% of penile SCCs. Grossly, they usually present as

an ulcerated irregular mass. On cut surface, they are tan, solid tumors deeply invasive into the corpus spongiosum or cavernosum (Figure 7.6). Micrcopically, there are separate or confluent solid tumoral nests composed of small basaloid cells, usually with central necrosis (comedo necrosis) or central abrupt keratinization (Figure 7.10(A) and (B)). Nucleoli are inconspicuous. There are numerous mitotic figures. Occasional palisading at the nest periphery may be noted but they are usually not as prominent as in basal cell carcinomas of the skin (Figure 7.10(B)). About two-thirds of the patients present with inguinal nodal metastasis.[35,36] The precancerous lesions most frequently associated with basaloid carcinomas are high-grade squamous intra-epithelial lesions of the warty or basaloid type (Figure 7.10(C)). These epithelial abnormalities are often found in the epithelium adjacent to the invasive cancer.

Unusual morphologic features of basaloid carcinomas: according with their common HPV etiology some tumors show mixed basaloid-warty features. The condylomatous component is superficial and papillary and the deep counterpart a typical basaloid carcinoma. There are deeply invasive nests with central keratinization or

A

B
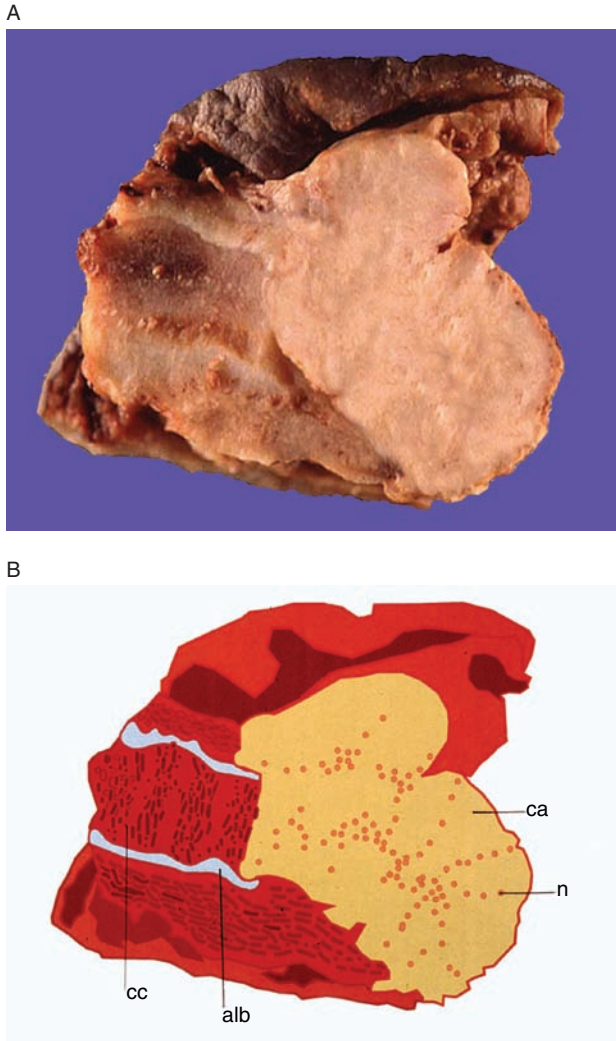
Figure 7.6
(A) and (B) Cut surface of tumors with a vertical pattern of growth (gross and diagram). This type of deeply invasive neoplasm is associated with a high rate of nodal regional metastasis. On microscopic examination, this case corresponded to a basaloid carcinoma. The areas of comedo-necrosis appeared as yellow dots. ca: carcinoma, n: foci of comedo necrosis, alb: albuginea, cc: corpus cavernosum.

comedo necrosis surrounded by clear cells with koilocytotic-like changes and peripheral small basaloid cells. These mixed tumors behave as basaloid carcinomas, with frequent nodal metastasis.[37] Another unusual morphologic presentation of basaloid carcinomas is that of a papillary lesion entirely composed of small basaloid cells (transitional-like papillary basaloid carcinoma). Deep portions of the tumor show the classical features of a basaloid carcinoma. Unlike other penile papillary tumors, the papillae are entirely composed of small cells simulating a transitional urothelial carcinoma.[38]

Condylomatous (warty) carcinomas

Warty carcinomas are slowly growing HPV-related tumors, grossly similar to giant condylomas but with a malignant histology and a

Figure 7.7
Microphotograph of a well-differentiated SCC illustrating the ample eosinophilic cytoplasm and relatively uniform nuclei of the neoplastic cells.
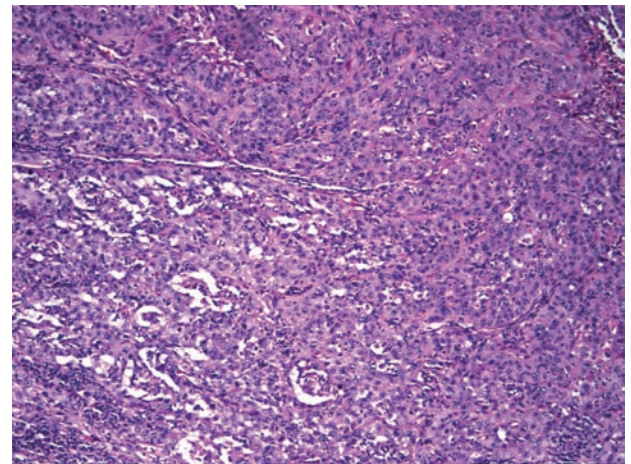
Figure 7.8
Poorly differentiated SCC showing sheets and confluent aggregates of neoplastic cells with high N/C ratio and scant or no keratinization.
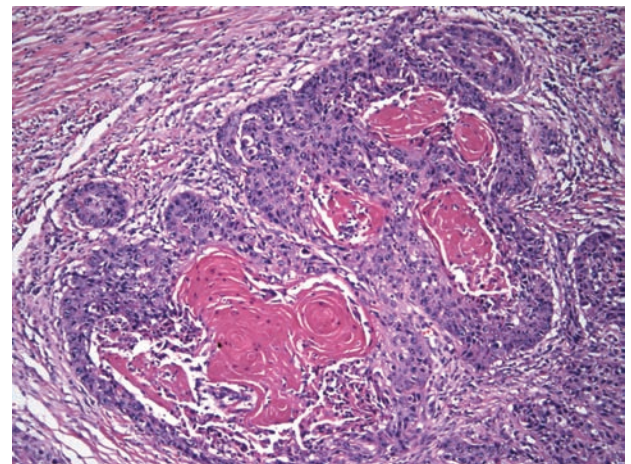
Figure 7.9
Moderately differentiated carcinoma. Most penile SCCs belong to this intermediate category.

A

B

C
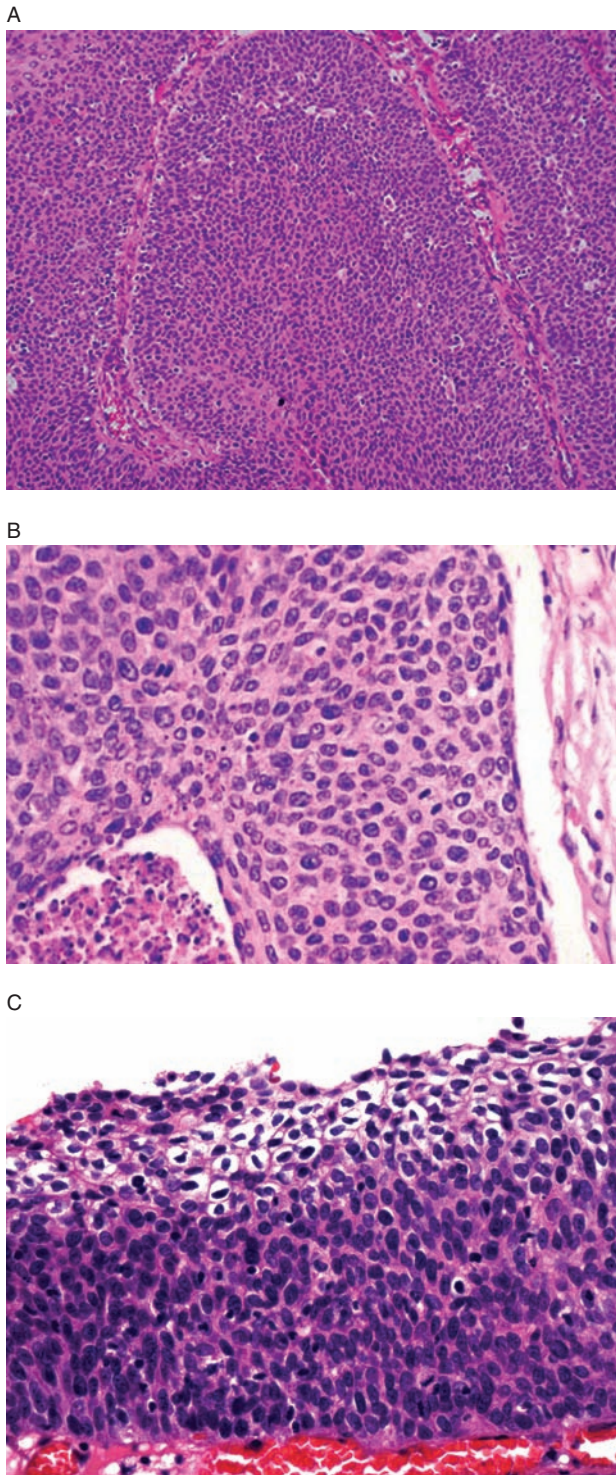
Figure 7.10

(A) and (B) Intermediate and high-power view of a basaloid carcinoma. The solid tumoral nests are composed of small basaloid cells with scant cytoplasm and numerous mitosis and apoptotic cells (A). Central areas of necrosis (comedo necrosis) and clefts between tumoral aggregates and stroma are a common finding in this subtype of penile SCC (B). (C) High-grade squamous intra-epithelial neoplasia of warty-basaloid type. There is full thickness keratinocytic atypia of the epithelium with basaloid cells in the lower half and prominent koilocytosis in the upper portion. These types of lesions are frequently found adjacent to invasive basaloid or warty carcinomas.

potential for nodal metastasis. They affect patients younger than the usual SCCs and the history of previous warts is frequent. Foreskin, coronal sulcus, and glans are usually involved. The cut surface shows a papillomatous growth usually penetrating into corpora spongiosa and cavernosa (Figure 7.11(A)). The interface of tumor and stroma is variable from broadly based to jagged and irregular. Histologically, the papillae are of the condylomatous type and of various shapes, round, ovoid or spiky, long or short, but always with a prominent central fibrovascular core and koilocytotic changes (Figures 7.11(B) and (C)). Unlike benign condylomas koilocytosis is not restricted to the surface but it is also present in deep invasive portions of the tumor (Figure 7.11(D)). Hyper- and parakeratosis and cellular pleomorphism, as well as clear cell features, may be prominent. Warty carcinomas may show variable amounts of non-invasive, mixed non-invasive–invasive or wholly invasive components. Combined lesions showing classical warty features adjacent to foci of SCC of the usual type or basaloid carcinoma are less frequent. The biological behavior of warty carcinomas is intermediate between that of other types of low-grade verruciform tumors (verrucous and papillary) and SCC of the usual type. Deeply invasive, high-grade warty carcinomas may be associated with inguinal nodal metastasis. The differential diagnosis is with verrucous and papillary carcinomas and with giant condylomas. Warty carcinomas lack the extreme differentiation of verrucous carcinomas and, unlike them, warty carcinomas usually show jagged and irregular deep borders. Low-grade warty carcinomas may be difficult to differentiate from papillary carcinomas; however, papillary carcinomas lack koilocytosis and typical condylomatous papillae and are in general better differentiated than warty carcinomas. Warty carcinoma in situ may be flat or papillary. When papillary, non-invasive warty carcinomas may be strikingly similar to giant condylomas, especially at low power. Warty carcinomas, however, are clearly malignant tumors.[39,40] Precursor lesions of warty carcinoma are thought to be high-grade squamous intra-epithelial neoplasms of warty (Figure 7.11(E)) and basaloid types. Often times, the precursor lesion shows mixed warty and basaloid features. Similar lesions are seen in the epithelium adjacent to basaloid carcinomas.

Verrucous carcinoma

Clearly described by Dr Lauren Ackerman in 1948 in the buccal mucosa,[41] verrucous carcinoma continues to pose diagnostic problems since other verruciform tumors share some of its characteristics. We had proposed a classification for penile verruciform neoplasms that is helpful to differentiate other verruciform lesions such as usual and giant condylomas, mixed verrucous carcinomas, warty carcinomas, and papillary carcinomas from pure (typical) verrucous carcinomas.[39] It is important to keep strict criteria in the diagnosis of verrucous carcinomas since typical verrucous carcinomas are virtually associated with no metastasis. We have found a spectrum of mixed or combined tumors with focal or significant verrucous carcinoma features, which need to be distinguished from typical verrucous carcinoma.[42] The most frequent combination is that of a verrucous carcinoma with foci of usual invasive SCC. These mixed or hybrid verrucous carcinomas have a metastatic rate of about 25%.[42] Another is the carcinoma cuniculatum with no proven risk of metastasis despite deep penetration of the tumor.[43] Verrucous carcinoma may also be associated with sarcomatoid carcinoma in a sporadic form or after radiation therapy.[44] HPV have been consistently reported as rare or negative in several studies.[22,23,45]

A

B

C

D

E
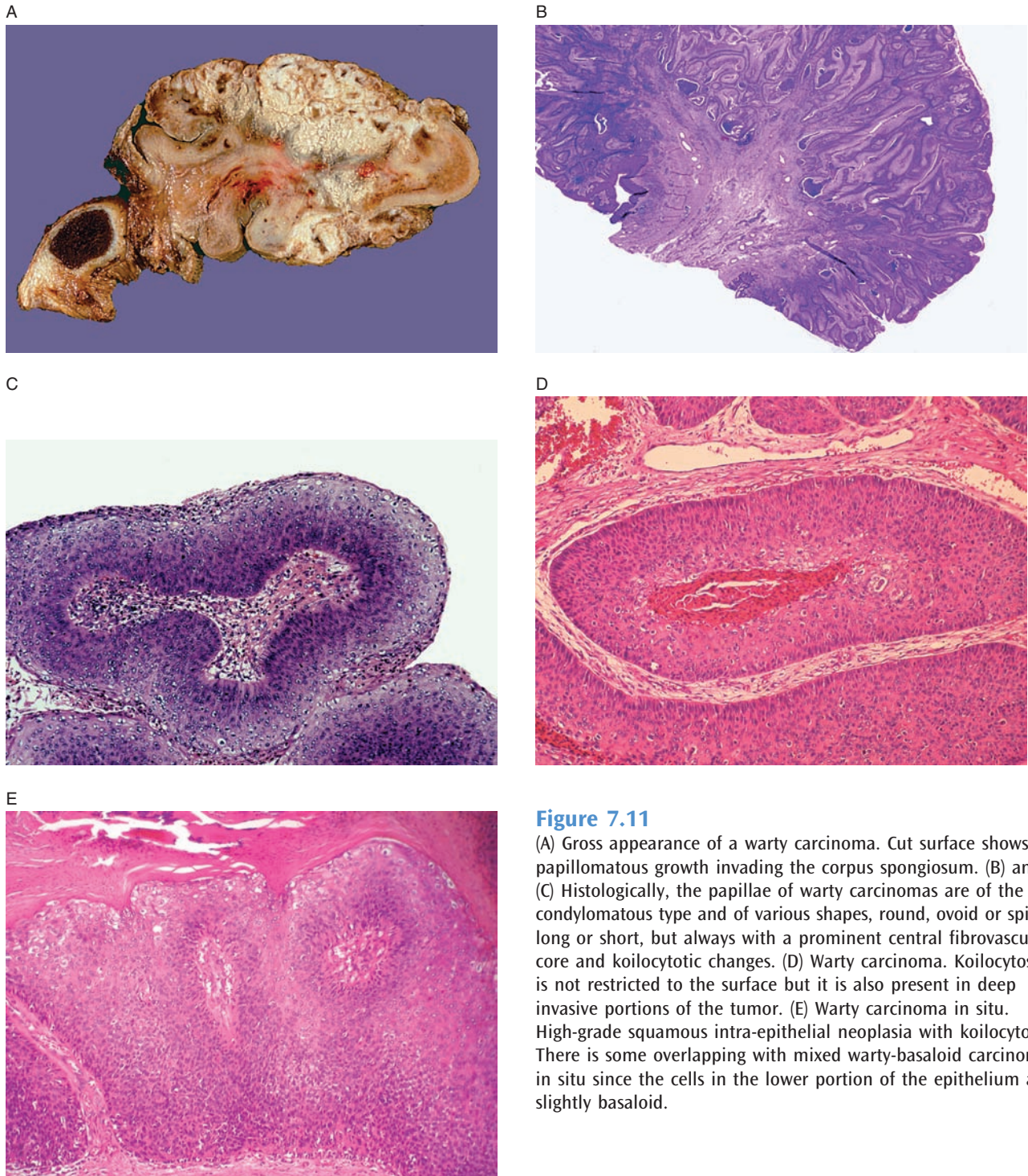
Figure 7.11

(A) Gross appearance of a warty carcinoma. Cut surface shows a papillomatous growth invading the corpus spongiosum. (B) and (C) Histologically, the papillae of warty carcinomas are of the condylomatous type and of various shapes, round, ovoid or spiky, long or short, but always with a prominent central fibrovascular core and koilocytotic changes. (D) Warty carcinoma. Koilocytosis is not restricted to the surface but it is also present in deep invasive portions of the tumor. (E) Warty carcinoma in situ. High-grade squamous intra-epithelial neoplasia with koilocytosis. There is some overlapping with mixed warty-basaloid carcinoma in situ since the cells in the lower portion of the epithelium are slightly basaloid.

Grossly, verrucous carcinomas are exophytic papillomatous tumors with some variation of the papillae configuration from multinodular with cobblestone appearance to filiform with spiky appearance (Figures 7.12(A) and (B)). The cut surface reveals a serrated surface and a broadly based limit between tumor and stroma (Figure 7.12(C)). The inferior border of the tumor is usually at the level of the thickened epithelium or in the lamina propria and only rarely penetrates into superficial corpus spongiosum or dartos. Histologically, the tumor shows extreme squamous differentiation

except for the presence of occasional atypical nuclei at the basal or parabasal layers (Figure 7.12(D)). There are papillomatosis, hyperorthokeratosis, acanthosis, and a broadly based interphase between tumor and stroma (Figures 7.12(D) and (E)). Koilocytosis is not present. Although some papillae may harbor fibrovascular cores, this is not a characteristic feature. The spaces between papillae are occupied by keratin-filled craters (Figure 7.12(F)) that on tangential cuts appear as keratin-filled pseudocysts. The stroma may show a dense lymphocytic infiltrate sometimes

A

B

C

D

E

F

G
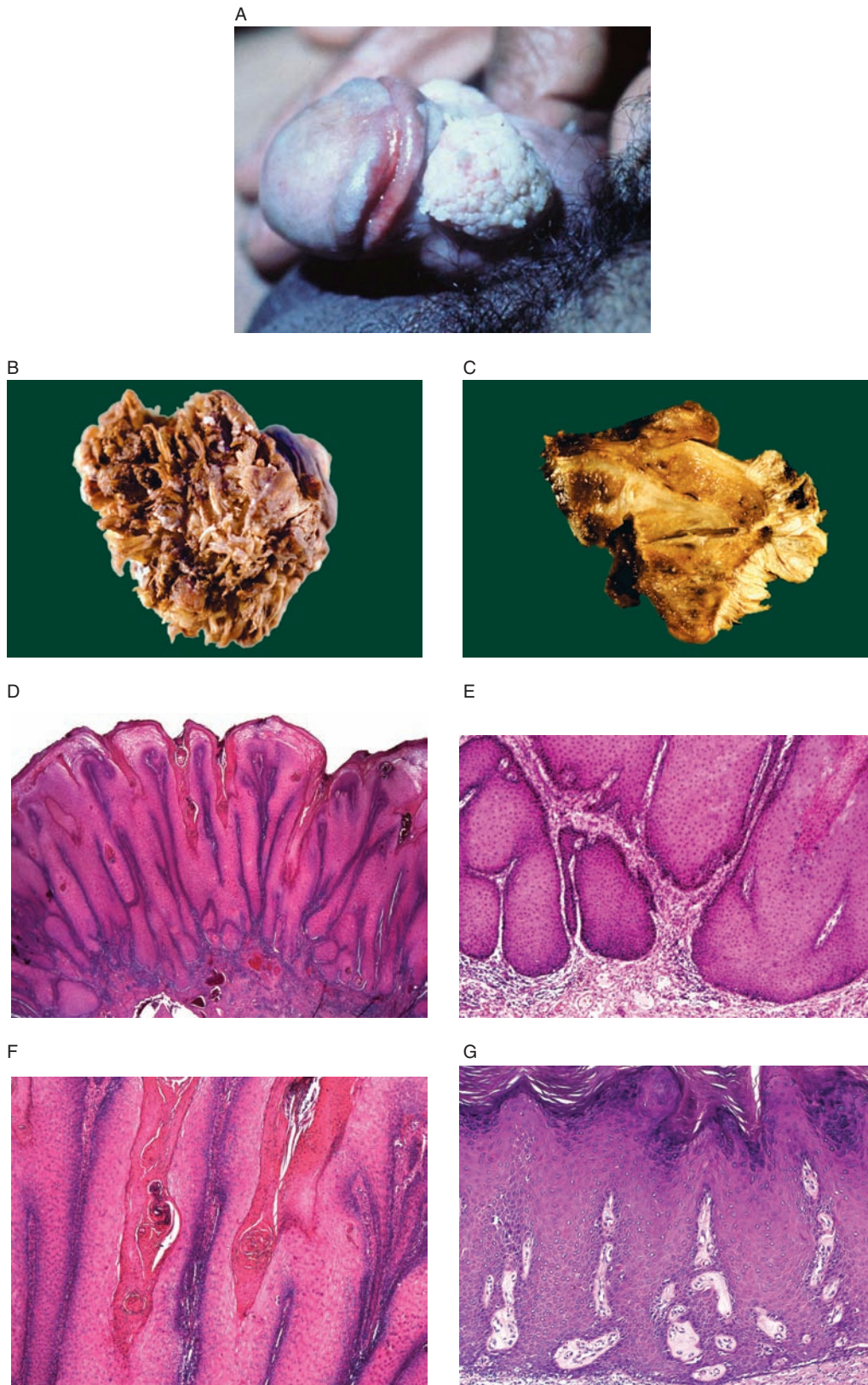
Figure 7.12
(A) Clinical picture of a case of multicentric verrucous carcinoma affecting the foreskin of a patient with long-standing lichen sclerosus. This example emphasizes the frequent association of preputial location, non-HPV-related tumors of low histologic grade, multicentricity, and lichen sclerosus. (B) Gross picture of a verrucous carcinoma showing an exophytic tumor with filiform, spiky papillae. (C) Cut surface of a verrucous carcinoma revealing a serrated surface and a broadly based, sharp deep border. (D) Histologic appearance of a verrucous carcinoma. There are papillomatosis, hyper-orthokeratosis, acanthosis, and a broadly based interface between tumor and stroma. Koilocytosis is not present. Although some papillae may harbor fibrovascular cores, this is not a characteristic feature. (E) The deep borders of verrucous carcinoma are typically broad and pushing. (F) Verrucous carcinoma is an extremely well-differentiated neoplasm. Keratin-filled valleys are seen between the papillae that, on tangential cuts, appear as acanthotic keratin-filled pseudocysts. (G) Squamous hyperplasia with verrucous features (verrucous hyperplasia) is often seen in the epithelium adjacent to verrucous carcinoma. Lichen sclerosus is another frequently found associated condition and may be etiologically related to verrucous carcinoma, as illustrated in this picture.

blurring the limits of tumor and underlying connective tissues. Associated lesions are squamous hyperplasia and low-grade squamous intra-epithelial lesion of the squamous or simplex type. The hyperplasia often adopts the features of verrucous hyperplasia (Figure 7.12(G)). Lichen sclerosus is another frequently found associated condition and may be etiologically related to verrucous carcinoma (Figures 7.12(A) and (G)).[46] Verrucous carcinoma is a slowly growing tumor but if insufficiently resected it is prone to local recurrences. We have not observed regional metastasis in typical (pure) lesions.

Papillary carcinoma, NOS

Papillary squamous cell carcinoma is the third type of penile low grade verruciform carcinoma. In general, a diagnosis of papillary carcinoma is achieved after verrucous and warty carcinomas have been ruled out.[47] Patients are about 60 years old. Tumors are grossly exophytic and large and affect glans, coronal sulcus, and foreskin.
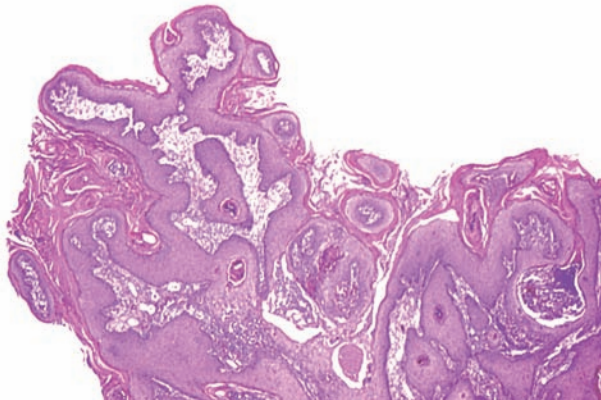
Figure 7.13
Papillary carcinomas are low-grade verruciform SCCs with variable complex arborescent papillae, without koilocytosis and with jagged, infiltrative, deep borders.

The cut surface shows a papillary neoplasm involving corpus spongiosum or dartos. Microscopically there is hyperkeratosis and papillomatosis. Papillae are variable and complex. The tip is either straight, undulated, spiky, or blunt. There is no koilocytosis. Histologic grade is low (Figure 7.13). The interface between tumor and stroma is characteristically jagged. Differential features from verrucous and warty carcinomas are based on the heterogeneity of the papillae, the lack of koilocytosis, and the jagged irregular interphase between tumor and stroma. The diagram in Figure 7.14 illustrates the differential features of these verruciform neoplasms. HPV studies may be necessary to differentiate some low-grade papillary neoplasms from low-grade warty carcinoma. Low-grade squamous intra-epithelial lesion and lichen sclerosus are frequently associated with papillary carcinomas. Papillary carcinomas are slow growing tumors with a low incidence of inguinal nodal metastasis.

Sarcomatoid carcinoma

Sarcomatoid carcinomas are aggressive penile neoplasms predominantly composed of spindle cells. They may arise de novo, after a recurrence of a usual SCC or following irradiation therapy of a verrucous carcinoma. They account for about 2–4% of all penile carcinomas.[48] They involve preferentially the glans but foreskin may also be affected. Like usual SCC, the mean patient age is around 60. Grossly, they are bulky 5–10 cm ulcerated or rounded polypoid masses which, on cut surface, almost invariably deeply invade into
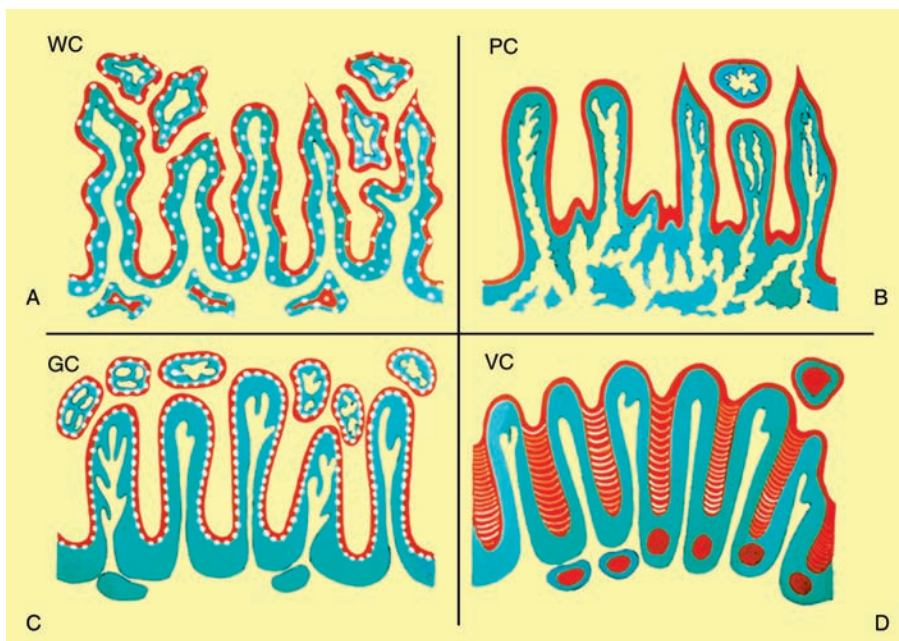
Figure 7.14
Diagram illustrating the differential features of verruciform lesions. The epithelium is seen in green, keratin in orange, and stroma in yellow. Koilocytosis is seen as white dots. (A) Warty (condylomatous) carcinoma (WC) with complex, irregular and arborescent papillae. Atypical cells and koilocytosis are seen throughout the lesion. The base is usually infiltrative and jagged. (B) Papillary carcinoma (PC) with irregular, arborizing papillae. There is no koilocytosis and the base of the neoplasm is irregular and infiltrative. (C) Giant condyloma (GC) showing arborizing, 'condylomatous' papillae with koilocytosis in the superior portion. There is no cytologic atypia and the base is regular, broad, and pushing. There may be some overlapping with low grade warty carcinomas. (D) Verrucous carcinoma (VC) shows thick, regular papillae separated by abundant keratin seen as keratin cysts when tangentially cut. There is no koilocytosis and the base of the tumor is broad and pushing.

A

B

C

D

E
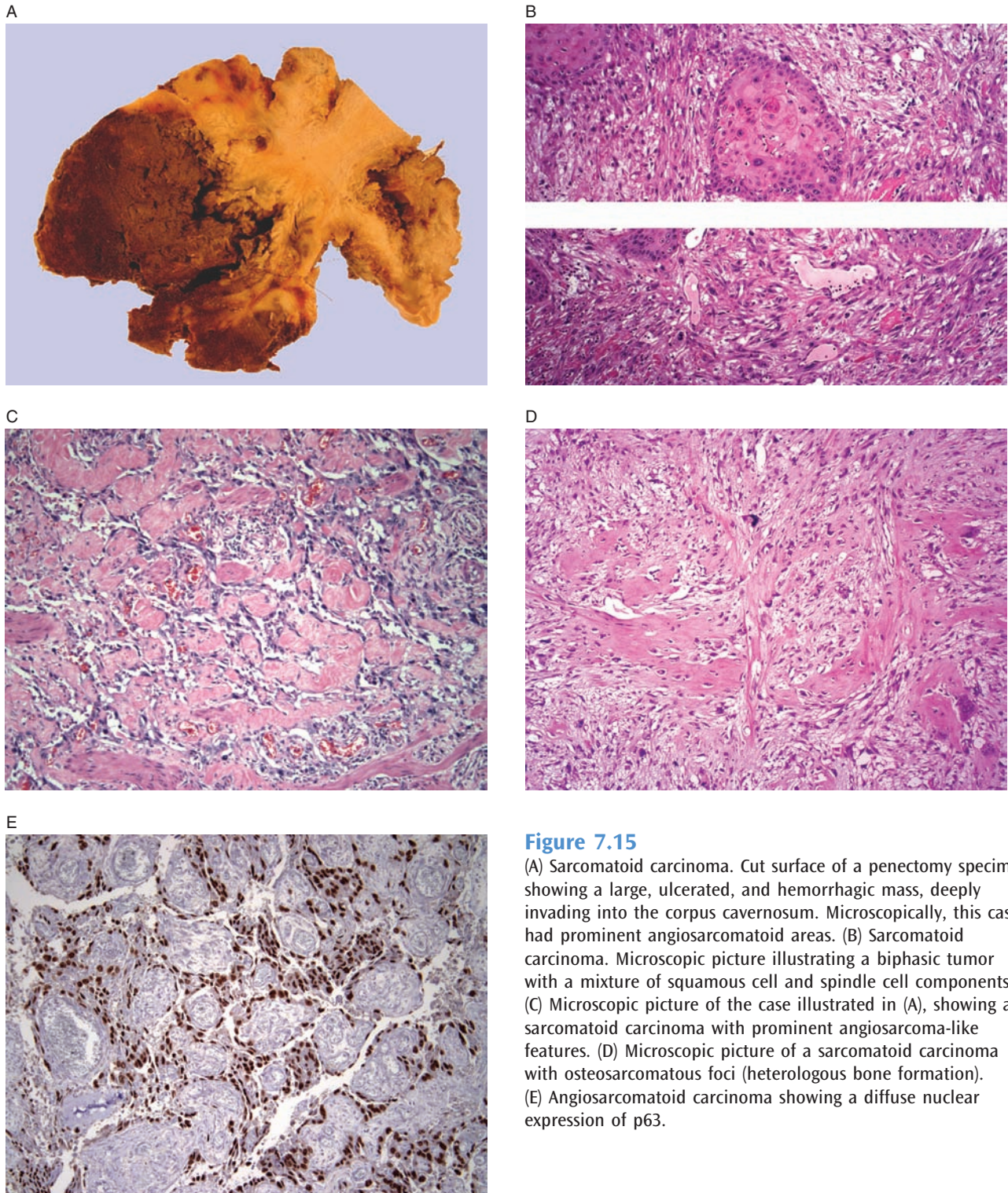
Figure 7.15

(A) Sarcomatoid carcinoma. Cut surface of a penectomy specimen showing a large, ulcerated, and hemorrhagic mass, deeply invading into the corpus cavernosum. Microscopically, this case had prominent angiosarcomatoid areas. (B) Sarcomatoid carcinoma. Microscopic picture illustrating a biphasic tumor with a mixture of squamous cell and spindle cell components. (C) Microscopic picture of the case illustrated in (A), showing a sarcomatoid carcinoma with prominent angiosarcoma-like features. (D) Microscopic picture of a sarcomatoid carcinoma with osteosarcomatous foci (heterologous bone formation). (E) Angiosarcomatoid carcinoma showing a diffuse nuclear expression of p63.

corpus cavernosum (Figure 7.15(A)). Microscopically there are variable proportions of squamous cell and spindle carcinoma (Figure 7.15(B)), usually the latter predominates. The sarcomatoid component may mimic fibrous histiocytoma, leiomyosarcoma, fibrosarcoma, mixosarcoma, epithelioid angiosarcoma, and classical angiosarcoma (Figure 7.15(C)). Heterologous bone (Figure 7.15(D)) and cartilaginous formation may be focally observed. The squamous component shows the morphology of the usual SCC but areas of

verrucous, papillary, or basaloid carcinoma may also be observed. HPV is usually negative. Differential diagnosis is with sarcomas or malignant melanomas. Inmunohistochemistry is useful for tumors with little or no epithelial component or in small biopsies. Besides lack of expression of melanocytic markers, we found cytokeratin 34BE12 and p63 positivity (Figure 7.15(E)) to be the most useful indication of epithelial lineage in sarcomatoid carcinomas. The spindle cell component is usually positive for vimentin. However, muscle

specific actin, smooth muscle actin, desmin, and mygenin are usually negative. Regional metastasis occurs in 85% of sarcomatoid carcinomas and mortality is high.[48]

Adenosquamous carcinomas

They are squamous cell carcinomas with focal or multifocal mucinous glandular differentiation (Figure 7.16). They are thought to arise from the epithelial surface of the glans, where foci of SSC in situ may be noted. Clinicopathologic features and outcome are similar to the usual SCC. The glandular component of this mixed tumor is usually a minor one. Adenosquamous carcinomas should be distinguished from mucoepidermoid, adenobasaloid, and pseudoglandular SCCs. In mucoepidermoid carcinomas, there are isolated cells or group of squamous cells containing mucin without glandular formation. In adenobasaloid tumors there are well-formed mucinsecreting glands, however the solid component is not the typical SCC but a basaloid carcinoma (unpublished personal observation). Pseudoglandular (adenoid or acantholytic) SCCs most frequently represent SCC of the usual type in which there is considerable

A
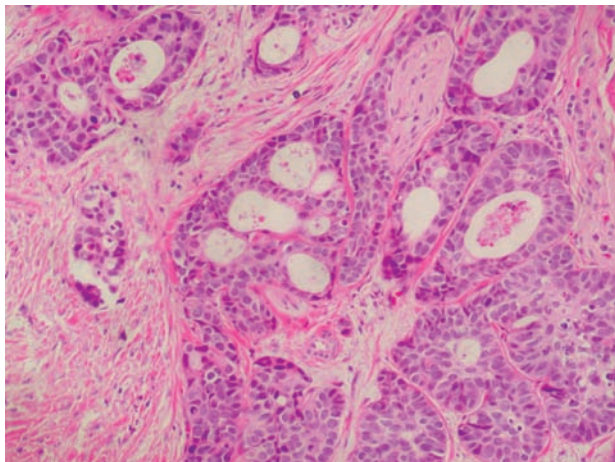
B
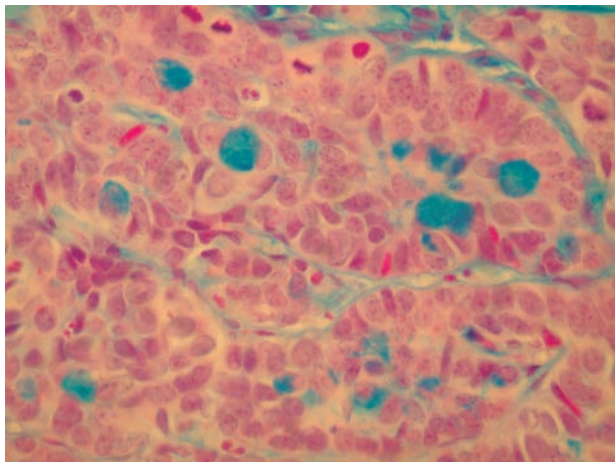
Figure 7.16
(A) and (B) Adenosquamous carcinomas with focal glandular differentiation with mucin production as highlighted with a mucicarmin stain.

dyskeratosis and acantholysis with secondary pseudolumina formation simulating glandular structures. The lack of mucin production and the presence of many desquamated acantholytic cells in the pseudolumina aid in the diagnosis of this variant. The few reported cases of adenosquamous carcinomas have behaved aggressively with frequent nodal metastasis.[49,50]

Other rare tumors

Giant condylomas

Exuberant exophytic benign condylomas reach large sizes after years of neglect. They may harbor atypias and invasive microcarcinomas. Patients are older than those with typical condylomas but younger than those with condylomatous (warty) carcinomas. Grossly, they are bulky, cauliflower-like tumors showing at cut surface a papillomatous growth with a sharp demarcation between tumor and stroma. The deep border of the tumor usually lies above the lamina propria without involvement of corpus spongiosum or dartos. Histologically, they are similar to usual condylomas except that some tumors depict destructive endophytic growing properties, fistulae to the skin, focal atypia, carcinoma in situ, or overt focally invasive squamous carcinomas.[38] The condylomatous papillae show a central fibrovascular core and superficial koilocytotic changes (Figure 7.17). We discourage the use of the term Buscke Lowenstein giant condyloma because this terminology has been used in the literature for various tumors such as verrucous and warty carcinomas, which are separate and distinctive tumor entities, thus creating unnecessary confusion.[51] The differential diagnosis is with common condyloma and with non-invasive warty carcinoma. Common condylomas affect younger patients, are smaller lesions, and are usually multiple, affecting not only the squamous epithelium of penile mucosal epithelial compartments but also the outer skin of the foreskin and shaft. Giant condylomas affect older patients and are usually bulky and unicentric. Non-invasive warty carcinoma may be macro- and microscopically very similar to giant condylomas. The main difference is that in warty carcinomas the atypical cells compromise the full epithelial thickness whereas atypical cells are not a feature of giant condylomas. There is probably some overlapping with very well-differentiated warty carcinomas that in some cases may be undistinguishable from giant condylomas.
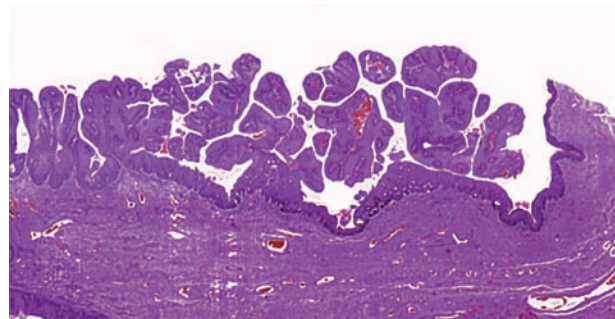
Figure 7.17
Giant condyloma showing the typical characteristics of a garden variety condyloma, but of larger size. This particular case extensively affected the foreskin and glans. However, the lesion is benign, showing extreme differentiation and no invasion.

Pseudohyperplastic carcinomas

Non-verruciform, low-grade squamous carcinomas preferentially affecting the foreskin of older patients (8th decade) and strongly associated with lichen sclerosus. There is extreme differentiation and in small biopsies the tumors mimic pseudoepitheliomatous hyperplasia. They are often multicentric and the second or third independent tumor may show some verrucous features. Grossly, they are flat or slightly elevated lesions measuring about 2 cm. Characteristic microscopic features are keratinizing nests of squamous cells with no or minimal atypia surrounded by a reactive stroma (Figure 7.18). This degree of differentiation is noted only in low-grade verruciform tumors such as verrucous or papillary cancers. The consistent association with lichen sclerosus suggests that this inflammatory condition may play a precancerous role. In a series of 10 cases, recurrence was noted in the glans of one patient who was circumcised for a multicentric carcinoma of the foreskin 2 years after diagnosis. No metastases were found in any of these cases.[52]

A

B

Carcinoma cuniculatum

Deeply penetrating albeit low-grade SCCs which because of their burrowing growth pattern were designated in the plantar region as epithelioma cuniculatum by Ayrd et al in 1954.[53] Seven cases of this unusual variant of SCC were reported in the penis. Mean age is 77 years. Grossly, the tumors were white-gray, exo-endophytic and papillomatous with a cobblestone or spiky appearance affecting the glans and extending to the coronal sulcus and foreskin (average size 6 cm). The hallmark of the lesion is noted on cut surface where deep invaginations of the tumor forming irregular, narrow, and elongated neoplastic sinus tracts that connect the surface tumor to deep anatomic structures are seen (Figure 7.19). Microscopically, the tumor partially resembles verrucous carcinoma with a bulbous front of invasion. There are, however, irregular foci of invasive squamous cell carcinoma of the usual type. It should be distinguished from classical verrucous carcinoma, which is extremely differentiated, rarely invades beyond the lamina propria, and its tumor front is sharply delineated. Despite the deep penetration, none of the reported carcinoma cuniculatum cases showed groin or systemic dissemination at time of diagnosis.[54]

Clear cell carcinoma

Clear cell features may be noted in squamous cell carcinomas. We have observed some examples of solid, poorly differentiated SCCs composed of PAS-positive clear cells and attributed the pattern to cytoplasmic hyperglycogenation, similar to the cervical uterine lesions.[1] Clear cells are also conspicuous in some warty carcinomas. A purported different penile tumor exclusively composed of clear cells and designated as clear cell carcinoma was reported from Austria.[55] They were large, exophytic, partially ulcerated and widely invasive, all located in the foreskin inner surface. Histologically, they were composed of large neoplastic cells with clear,

Figure 7.18
(A) Pseudohyperplastic squamous cell carcinoma. Low-power view of this extremely well-differentiated carcinoma that may be confused with pseudoepitheliomatous hyperplasia. (B) Lichen sclerosus is consistently seen adjacent to pseudohyperplastic carcinomas. There is low-grade atypia in the hyperplastic epithelium, suggesting that lichen sclerosus may play a precancerous role.

Figure 7.19
Carcinoma cuniculatum. The hallmark of the lesion is noted on cut surface: deep invaginations of the tumor forming irregular, narrow, and elongated neoplastic sinus tracts connecting surface tumor to deep anatomic structures.

PAS-positive cytoplasm. All carcinomas harbored HPV 16. All five patients had groin cystic metastasis also showing clear cells. Two patients were reported as alive and the rest either dead or with evidence of disease at last follow-up.[55]

Grading system and other prognostic parameters

Pathologic factors affecting patient outcome are multiple and it is difficult to ascertain the independent validity of the factors. Commonly cited factors are histologic grade, anatomic site and size of primary tumor, growth patterns, subtypes of SCC, tumor depth or thickness, positive margins of resection, and perineural and vascular invasion.[56] There are also some molecular factors, which may be related to outcome.

Histologic grade

Histologic grade is important to predict groin metastasis and dissemination of penile cancer[56–63] and there are several grading systems. The most commonly used approach is to classify invasive penile cancer into grade 1, well-differentiated with no evidence of anaplastic cells; grade 2, moderately differentiated with anaplastic cells comprising less than 50% of the tumor, and grade 3, poorly differentiated with more than 50% of the neoplasm composed of anaplastic cells. A method which we were using in our daily practice is to consider as grade 1, the extremely well-differentiated carcinomas (verrucous, some papillary and pseudohyperplastic variants of SCCs would qualify for this grade), grade 3 when more than 30% of the cells are anaplastic, and grade 2 the remainder of the tumors. Grading both extremes of the spectrum is simple and reproducible. It is not uncommon to find multiple grades associated in the same specimen and a judicious evaluation is always necessary to determine the importance of each grade group for the overall grade given to a tumor. Recently, we found that about half of penile SCCs are heterogeneous, showing more than one grade in the same specimen,[64] and that any proportion of grade 3 appears to affect patient outcome.[65] It is possible that a 2-grade system, low- and high-grade, would suffice for tumor grading. Areas of higher tumor grade in heterogeneous neoplasms are ubiquitous and can be found near the surface or in the deepest point or front of invasion.

Anatomic location

Tumors may originate in the glans, foreskin, or coronal sulcus. Tumors affecting exclusively the foreskin tend to be superficially invasive lesions of low histologic grade and, for these reasons, rarely associated with nodal metastasis. Tumors affecting the glans are of higher histologic grade, usually infiltrate deeper anatomic layers, and show higher incidence of regional metastasis.[34] Tumors of the sulcus are very rare. Under-recognized neoplasms are those of distal urethra-perimeatal transition. They appear to be more related to penile than to urothelial neoplasia.[66] They are papillary squamous lesions composed of small basaloid or 'transitional' cells. The majority of these lesions are HPV-related, of variable histologic grade,

non-invasive, and associated with favorable outcome.[67–72] They need to be distinguished from condylomas, which are not infrequent at these sites.

Size of primary tumor

The incidence of lymph node metastasis is low in patients with tumors measuring up to 2 cm and also in tumors measuring more than 4 cm (about 30%), whereas in medium size tumors (2–4 cm) it is significantly higher (68%).[55] This paradox may be explained by the contrasting large size and low incidence of metastasis in verruciform tumors. Verruciform tumors (verrucous, papillary NOS, and condylomatous/warty carcinomas) are rarely associated with metastasis despite their frequent large size. Tumor size becomes a significant prognostic marker when verruciform neoplasms and superficial spreading SCCs are excluded from the evaluation.

Patterns of growth

There is a correlation between growth pattern and outcome. Regional spread is very unusual in verruciform and highly prevalent in vertical growth tumors. Superficial spreading and multicentric cancers show a low to moderate frequency of regional spread.[33,57]

Histologic subtypes

There is a correlation between histologic subtype of squamous cancer and rates of regional or systemic dissemination, although on multivariate analysis histologic type appears to be less important than other factors. Tumors can be separated into three risk categories for metastasis, based on their histologic type. In the low-risk group are the usual SCCs with superficial spreading pattern of growth, verruciform, and pseudohyperplastic carcinomas, all low-grade SCCs. Tumors with high metastatic potential are basaloid, sarcomatoid, and solid poorly differentiated SCCs. The majority of these neoplasms present with a high-grade histology and invasion of the corpus cavernosum or at least the deep portion of the corpus spongiosum. More than half of penile carcinomas, however, would fall in an intermediate category of metastatic risk. This group includes most usual squamous cell carcinomas, some mixed neoplasms, and pleomorphic variants of condylomatous (warty) carcinomas.[73]

Tumor depth of invasion and thickness

There is a correlation between depth of invasion and outcome in penile cancers. Minimal risk for metastasis was reported for tumors invading less than 5 mm.[74,75] In a study of 35 patients with penile carcinomas, we found no metastasis in carcinomas invading no more than 5 mm and 53% and 69% incidence of nodal metastasis in tumors invading an average depth of 6 and 12 mm, respectively.[76] Similar findings were reported in a recent series.[77] We have shown

that the histologic grade appears to be more important than depth of invasion as a predictor of groin metastasis.[77]

In a pathologic evaluation of hundreds of resected specimens for penile SCC, we observed a single case of metastasis from a tumor invading 2 mm into the lamina propria. A brain metastasis was reported associated with a small and superficial tumor.[78]

Anatomic levels of invasion

The anatomic levels of the penis vary in the different anatomic compartments. In the glans, the levels are epithelium, lamina propria, corpus spongiosum, and corpus cavernosum. The tunica albuginea is part of the corpus cavernosum. In the foreskin the levels are epithelium, lamina propria, dartos, and skin.[79] The risk of metastasis is proportionally related to progressive invasion of deeper anatomic layers. Superficial tumors invading the lamina propria or the superficial portion of the corpus spongiosum (less than 5 mm in thickness) have low metastatic potential while lesions invading deeply into the corpus spongiosum or cavernosum (more than 5 mm) are associated with high metastatic rate.[74,76]

Positive resection margins

Like with other tumors, the presence of positive resection margins adversely affects prognosis in patients with penile SCCs. The most commonly affected margin is the urethral margin of resection including periurethral tissues and the Bucks' fascia. In partial penectomies we recommend submitting three margins: (a) urethra and periurethral tissues, (b) skin of the shaft, and (c) corpora cavernosa (Figure 7.20). The most important margin corresponds to the urethra and periurethral tissues (lamina propria of the urethra, peri-
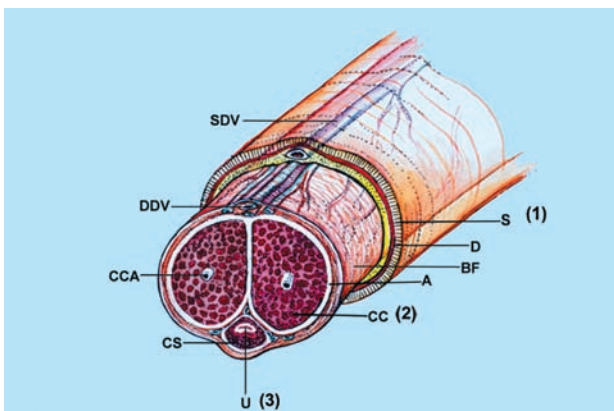
Figure 7.20
In partial penectomies we recommend submitting at least 3 separate margins: (1) skin of the shaft, (2) corpora cavernosa, and (3) urethra and periurethral tissues, which include the periurethral lamina propria, corpus spongiosum, tunica albuginea and Bucks' fascia. S: skin of the shaft, D: dartos, BF: Bucks' fascia, A: albuginea, CC: corpus cavernosum, U: urethra, CS: corpus spongiosum, SDV: superficial dorsal vein, DDV: deep dorsal vein.

urethral corpus spongiosum, and penile fascia), preferred sites of margin involvement as shown in a prior study.[80] Often, the tumoral involvement of the resection margin may be identified only at a microscopic level. Sometimes, tumor emboli are found in periurethral lamina propria or corpus spongiosum. An underrecognized site of positive margin is the fascia of Buck, composed of loose fibrous tissue containing numerous vascular structures and nerves. When dealing with a circumcision specimen, it is important to identify and submit the coronal sulcus margin since involvement of this margin by the carcinoma may warrant additional surgery to prevent recurrences. A sound knowledge of penile anatomy is necessary to improve tha handling and pathology reporting of circumcision and penectomy specimens.[80,81]

Vascular and perineural invasion

Vascular invasion, lymphatic or venous, adversely affects prognosis of penile cancer.[82,83] Venous invasion, less frequent, indicates a more advanced stage of the disease and it is related to the compromise of the specialized erectile venous structures of corpora spongiosa and cavernosa. There is limited information on the significance of perineural invasion as a prognostic factor in penile cancer. In a study of 35 penectomy specimens with regional nodal dissection we found perineural invasion in 18 (51%) of the cases, 10 of which were associated with nodal metastasis.[56] In the same study, there were 17 patients without regional metastasis and perineural invasion was present in only 1 of these patients. Perineural invasion may also be an important adverse prognostic factor.

Scoring and prognostic index systems

Maiche et al designed a scoring system based on keratinization, mitotic activity, cellular atypia, and presence of inflammatory cells. They proposed a 4-grade system and found good correlation with clinical staging.[84] Based on the combined value of level of invasion and histologic grade to predict metastasis and mortality in invasive SCCs,[85,86] a prognostic index was also proposed.[56] The index is represented by a number from 2 to 6 and it is calculated by adding numerical values given to the histologic grade (1, 2 and 3) and to anatomic levels of invasion (1 for lamina propria, 2 for corpus spongiosum or dartos, and 3 for corpus cavernosum or skin in the glans and foreskin, respectively). Patients with indexes 2 and 3 show virtually no risk for metastasis, patients with index 4 have low risk and patients with indexes 5 and 6 have high risk for metastatic disease and mortality. The method is to be used in resected specimens but not in biopsies. Biopsies are usually useful for the diagnosis of SCC; however, additional information such as level of invasion, histologic grade, and presence of vascular invasion is better assessed in the resection specimen. Due to the limitations of the biopsies, imaging techniques such as ultrasonography and magnetic resonance imaging may be useful tools to stage tumors after a diagnosis of SCC has been rendered by biopsy and the best therapeutic approach needs to be planned. In our clinical practice, after a prognostic index was calculated in the resection specimen and because of its high negative predictive value, patients with indexes 2 and 3 are not subjected to inguinal lymph node dissection whereas those with indexes 5 and 6 undergo groin node dissection. The biological behavior of tumors

with a prognostic index 4 is more difficult to predict. In these cases, careful evaluation of the patients' clinical characteristics and additional pathologic features of the tumor need to be taken into consideration before making the decision on groin dissection.[88,89] Appropriate lymph node management is important since survival rates significantly decrease in the presence of persistent regional metastasis.

Molecular and other prognostic factors

The use of molecular prognostic factors is not yet a common practice in the pathologic management of penile cancers. There are several studies of molecular prognostic factors with various results.[90–94] Ploidy was not found to be useful to predict prognosis in penile carcinomas.[91] p53 was considered an independent risk factor for metastasis and final outcome in some studies, but not in others.[92–94] Although HPV appears to be more frequent in higher-grade neoplasms, it does not appear to be significant per se in predicting outcome. This finding may be related to the fact that tumors known for high and low risk for metastasis, such as the basaloid and warty carcinomas, are HPV-related. Marked peritumoral infiltration of eosinophils was reported to be linked with improved survival in patients with penile carcinoma in one study.[95]

Routes of local spread and TNM staging

Penile carcinomas predictably spread to local, regional, and systemic sites. Initial local invasion is of subepithelial lamina propria, dartos, or superficial corpus spongiosum (less than 5 mm). Later invasion is of deep corpus spongiosum, tunica albuginea, and corpora cavernosa. Urethral invasion is not unusual in either early or late stages. Intrapenile satellitosis (nodular aggregates of neoplastic cells, usually of higher histologic grade that are separate from the main tumor) appear to be a late phenomenon and related to aggressive tumor behavior. Extrapenile regional dissemination occurs in superficial and deep inguinal lymph nodes. The purported first site of nodal metastasis is or are 1 or 2 superficial inguinal lymph nodes located in the upper inner quadrant (sentinel lymph node/s).[96,97] However, some tumors will directly metastasize to deep inguinal nodes.[98] Skip metastasis from primary tumor to pelvic nodes sparing the groin is extremely unusual.[7] Extrapenile skin satellitosis may be present at the moment of initial consultation or it may be a sign of recurrence after penectomy and groin dissection. In any case, it is a sign of advanced clinical stage and bad prognosis. Although penile carcinoma is considered a local regional disease, widespread dissemination occurs in at least a third of the patients. Main sites of metastatic involvement at autopsy are lymph nodes (pelvic, retroperitoneal, and mediastinal), liver, lungs, bone, and heart myocardium.[99] TNM staging system is depicted in Table 7.1.[100]

Precancerous lesions

A heterogeneous spectrum of epithelial alterations and atypical lesions may affect the squamous epithelium of the anatomic compartments of the penis. The terminology utilized to define these lesions is variable. The few pathologic studies of penile precancerous lesions are mostly related to high-grade intra-epithelial lesions and HPV and the information on low-grade atypical lesions is limited.[101,102] In a study of 288 cases, we described the morphologic features of all epithelial alterations, benign and atypical, low- and high-grade, associated with invasive squamous cell carcinoma of the penis and documented their relation with each other and with subtypes of invasive carcinoma.[103] The lesions were classified as squamous hyperplasia, and squamous intra-epithelial lesions of low and high grade (LGSIL and HGSIL). In LGSIL, atypia was confined to the lower third and in HGSIL atypical cells affected at least two-thirds of the squamous epithelium.[103] Subtypes of SIL were squamous, warty, basaloid, warty-basaloid, and papillary. Squamous hyperplasia, the most common lesion, was found in 83% of the cases followed by LGSIL (57%) and HGSIL (44%). In 62% of the cases, more than one associated lesion was present per specimen. A sequence from squamous hyperplasia to low-grade to high-grade SIL was also noted in some cases. In other cases, and especially in well-differentiated invasive SCCs, the only associated and contiguous epithelial lesion was squamous hyperplasia (Figure 7.21). LGSIL was associated with all types of carcinomas except basaloid tumors. HGSIL was present in two-thirds of invasive warty, basaloid, and mixed warty-basaloid tumors (especially the basaloid, warty, and mixed warty-basaloid SIL variants) (Figures 7.10 (C) and 7.11 (E)) and in about half of usual SCCs (especially the squamous variant).[103] HGSIL was not observed associated with papillary, verrucous, and pseudohyperplastic SCCs; these well-differentiated SCCs were seen adjacent and contiguous to squamous hyperplasia and LGSIL and

Table 7.1 Tumor-Node-Metastasis (TNM) classification for SCC of the penis

Stage	Description
Tumors	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Ta	Non-invasive verrucous carcinoma
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades corpus spongiosum or cavernosum
T3	Tumor invades urethra or prostate
T4	Tumor invades other adjacent structures
Node	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single superficial, inguinal lymph node
N2	Metastasis in multiple or bilateral superficial inguinal lymph nodes
N3	Metastasis in deep inguinal or pelvic lymph node(s), unilateral or bilateral
Metastasis	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Additional descriptor
The m suffix indicates the presence of multiple primary tumors and is recorded in parentheses
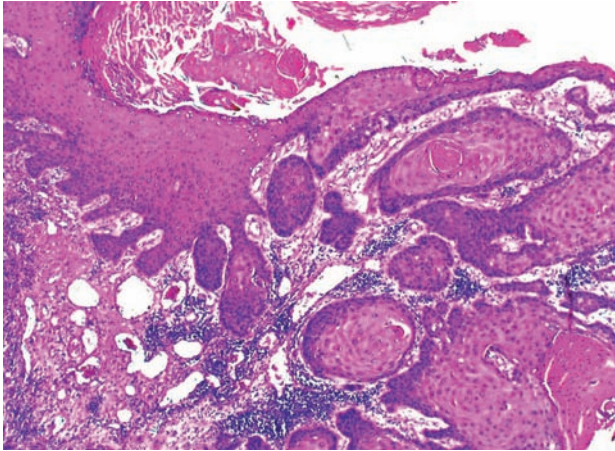
Figure 7.21
Microscopic picture illustrating squamous hyperplasia contiguous to a well-differentiated invasive SCC.

not infrequently the adjacent mucosa showed changes of lichen sclerosus. It is interesting to note the morphologic correlation of special types of invasive carcinomas with subtypes of SIL and squamous hyperplasia. The high frequency of squamous hyperplasia and LGSIL in usual, verrucous, papillary, and pseudohyperplastic carcinomas suggests they may be precursors of the aforementioned SCC variants. Likewise, the significant association and histologic similarities between HGSIL of the basaloid, warty, or mixed forms with their invasive counterparts indicates these lesions are their likely precursors.

Lichen sclerosus, typical and atypical

Lichen sclerosus, also known in the penis as balanitis xerotica obliterans, is an unusual, chronic mucocutaneous condition that may affect all the penile epithelial compartments including distal urethra, but it is more frequent in the foreskin inner surface. An association between penile lichen sclerosus and penile SCC has been suggested by a prospective study in which 9.3% of 86 patients with long-standing lichen sclerosus developed malignant changes.[104,105] In a review of 68 penile carcinomas we found histopathologic evidence of lichen sclerosus adjacent to the tumor in 33% of the cases (46%), and the incidence is higher (70%) in carcinomas exclusively affecting the foreskin.[34] We have found a preferential association between lichen sclerosus and non-HPV-related SCC variants, such as usual, verrucous, papillary, pseudohyperplastic, and sarcomatoid. The finding of hyperplastic and atypical changes in the epithelial component of a significant number of specimens with lichen sclerosus adjacent to invasive SCC (Figure 7.18(B)) is noteworthy. These findings suggest that lichen sclerosus may represent a preneoplastic condition for at least a subset of penile cancers, in particular those not related to HPV.[46]

References

1. Young RH, Srigley JR, Amin MB et al. Tumors of the Prostate Gland, Seminal Vesicles, Male Urethra and Penis. Atlas of Tumor Pathology, 3rd series (Fascicle 28). Washington DC: Armed Forces Institute of Pathology; 2000.

2. Velazquez EF, Cold CJ, Barreto JE et al. Penis. In: Mills SE, ed. Histology for Pathologists, 3rd edn. Lippincott Williams & Wilkins, 2006.

3. Dillner J, von Krogh L, Horenblas S et al. Etiology of squamous cell carcinoma of the penis. Scand J Urol Nephrol Suppl 205: 189–93.

4. Parkin DM, Miur CS, Whelar SL et al. Cancer Incidence in Five Continents. Volume VI. IARC Scientific Publications 120. Lyon, France: IARC; 1992.

5. Lebron RF, Riveros M. Geographical pathology of cancer of the penis. Cancer 1963; 15: 798–810.

6. Prener A, Storm HH, Nielsen NH. Cancer of the male genital tract in Circumpolar Inuit. Acta Oncol 1996; 35: 589–93.

7. Cubilla AL, Dillner J, Schellhammer PF et al. Malignant Epithelial Tumors. In: Tumors of the Penis. Pathology & Genetics. Tumors of the Urinary System and Male Genital Organs. Lyon, France: IARC Press, WHO; 2003.

8. Yeole BB, Jussawalla DJ. Descriptive epidemiology of cancers of the male genital organs in greater Bombay. Ind J Cancer 1997; 34: 30–9.

9. Maiche AG. Epidemiological aspects of cancer of the penis in Finland. Eur J Cancer Prev 1992; 1: 153–8.

10. Santos Arrontes D, Fernandez Arjona M et al. Epidemiological analysis of the squamous cell carcinoma of the penis in a 90,000 inhabitants health area. Arch Esp Urol 2005; 58: 898–902.

11. Cubilla AL, Tamboli P, Ro JY et al. Geographical comparison of subtypes of squamous cell carcinoma of the penis from regions of high low incidence. Lab Invest 2000; 80: 97A.

12. Persky L. Epidemiology of cancer of the penis. Recent results. Cancer Res 1977; 60: 97–109.

13. Tsen HF, Morgenstern H, Mack T et al. Risk factors for penile cancer: results of population-based case control study in Los Angeles County (United States). Cancer Causes Control 2001; 12: 267–77.

14. Brinton LA, Li JY, Rong SD et al. Risk factors for penile cancer: results from a case-control study in China. Int J Cancer 1991; 20: 504–9.

15. Maden C, Sherman KJ, Beckman AM et al. History of circumcision, medical conditions and sexual activity and risk of penile cancer. J Natl Cancer Inst 1993; 85: 19–24.

16. Dodge OG, Linsell CA. Carcinoma of the penis in Ugandan and Kenyan Africans. Cancer 1963; 16: 1255–63.

17. Hellberg D, Valentin J, Eklund T et al. Penile cancer: is there an epidemiological role for smoking and sexual behaviour? BMJ 1987; 295: 1306–8.

18. Seyam RM, Bissada NK, Mokhatar AA et al. Outcome of penile cancer in circumcised men. J Urol 2006; 175: 557–61.

19. Pukkala E, Weiderpass E. Socio-economic differences in incidence rates of cancer of the male genital organs in Finland, 1971–95. Int J Cancer 2002; 102: 643–8.

20. Nandakumar A, Gupta PC, Gangadharan P et al. Geographic pathology revisited: development of an atlas of cancer in Ind. Int J Cancer 2005; 116: 740–54.

21. Ayala GE, Barreto JE, Rodríguez I et al. Human papillomavirus-related lesions of the penis. Path Case Rev 2005; 10: 14–20.

22. Gregoire L, Cubilla AL, Reuter VE et al. Preferential association of human papillomavirus with high-grade histologic variants of penile invasive squamous cell carcinoma. J Natl Cancer Inst 1995; 87: 1705–9.

23. Rubin MA, Kleter B, Zhou M et al. Detection and typing of human papillomavirus DNA in penile carcinoma: evidence for multiple independent pathways of penile carcinogenesis. Am J Pathol 2001; 159: 1211–18.

24. Picconi MA, Eijan AM, Distefano AL et al. Human papillomavirus (HPV) DNA in penile carcinomas in Argentina: analysis of primary tumors and lymph nodes. J Med Virol 2000; 61: 65–9.

25. Bleeker MC, Howewoning CJ, Voorhorst FJ et al. HPV-associated flat penile lesions in men of a non-STD hospital population: less frequent and smaller in size than in male sexual partners of women with CIN. Ont J Cancer 2005; 113: 36–41.

26. Aboulafia DM, Gibbons R. Penile cancer and human papillomavirus (HPV) in a human inmunodeciency virus (HIV)-infected patient. Cancer Invest 2001; 19: 266–72.

27. Frisch M, Biggar RJ, Goedert JJ. Human papillomas virus-associated cancer in patients with human immunodeficiency virus infection

and acquired immunodeficiency syndrome. J Nat Cancer Int 2000; 20: 1500–10.

28. Alves G, Macrini CM, de Souza Nascimiento P et al. Detection and expression of Epstein–Barr virus (EBV) DNA in tissues from penile tumors in Brazil. Cancer Lett 2005; 227: 223–4.

29. Velazquez EF, Cubilla AL. Morphological features of penile squamous cell carcinoma. Anatomical, pathological and viral studies in Paraguay (1993–2006). Anal Quant Cytol Histol 2006 (in press).

30. Magoha GA, Ngumi ZW. Cancer of the penis at Kenyatta National Hospital. East Afr Med J 2000; 77: 526–30.

31. Rippentrop JM, Joslyn SA, Konety BR. Squamous cell carcinoma of the penis: evaluation of data from the surveillance, epidemiology, and end results program. Cancer 2004; 101: 1357–63.

32. Velazquez EF, Bock A, Soskin A et al. Preputial variability and preferential association of long phimotic foreskins with penile cancer: an anatomic comparative study of types of foreskin in a general population and cancer patients. Am J Surg Pathol 2003; 27: 994–8.

33. Cubilla AL, Barreto J, Caballero C et al. Pathologic features of epidermoid carcinoma of the penis. A prospective study of 66 cases. Am J Surg Pathol 1993; 17: 753–63.

34. Oertel J, Duarte S, Ayala J et al. Squamous cell carcinoma exclusive of the foreskin: distinctive association with low grade variants, multicentricity and lichen sclerosus. Mod Pathol 2001; 15: 175A.

35. Cubilla AL, Reuter VE, Gregoire L et al. Basaloid squamous cell carcinoma: a distinctive human papillomavirus related penile neoplasm. A report of 20 cases. Am J Surg Pathol 1998; 22: 755–61.

36. Tran TA, Tamboli P, Ayala G et al. Basaloid squamous cell carcinoma of the penis: a clinicopathologic study of 11 cases. Lab Invest 2000; 106A.

37. Tamboli P, Tran TA, Ayala AG et al. Mixed basaloid-condylomatous (warty) squamous cell carcinomas (SCC) of penis. A report of 17 cases. Lab Invest 2000; 80: 107 A.

38. Cubilla AL, Velazquez EF, Ayala G et al. Identification of prognostic pathologic parameters in squamous cell carcinoma of the penis. Significance and difficulties. Pathol Case Rev 2005; 10: 3–13.

39. Cubilla AL, Velazquez EF, Reuter VE et al. Warty (condylomatous) squamous cell carcinoma of the penis. Am J Surg Pathol 2000; 24: 505–12.

40. Bezerra AL, Lopes A, Landman G et al. Clinicopathologic features and human papillomavirus DNA prevalence of warty and squamous cell carcinoma of the penis. Am J Surg Pathol 2001; 25: 673–8.

41. Ackerman LV. Verrucous carcinoma of the oral cavity. Surgery 1948; 23: 670–8.

42. Cubilla AL, Velazquez EF et al. The heterogeneous spectrum of penile verrucous carcinoma. Morphological features of classical and mixed variants. A report of 36 cases. Mod Pathol 2004; 17: 610 A.

43. Barreto JE, Velazquez EF, Ayala E et al. Carcinoma cuniculatum of the penis: a distinctive variant of squamous cell carcinoma. Report of 7 cases. Am J Surg Pathol 2006. In press.

44. Fukunaga M, Yokoi K, Miyazawa Y et al. Penile verrucous carcinoma with anaplastic transformation following radiotherapy. A case report with human papillomavirus typing and flow cytometric DNA studies. Am J Surg Pathol 1994; 18: 501–5.

45. Masih AS, Stoler MH, Farrow GM et al. Penile verrucous carcinoma: a clinicopathologic, human papillomavirus typing and flow cytometric analysis. Mod Pathol 1992; 5: 48–55.

46. Velazquez EF, Cubilla AL. Lichen sclerosus in 68 patients with squamous cell carcinoma of the penis: frequent atypias and correlation with special carcinoma variants suggests a precancerous role. Am J Surg Pathol 2003; 27: 1448–53.

47. Chaux A, Velazquez EF, Torres J et al. Papillary squamous cell carcinoma of the penis. A report of 18 cases. Mod Pathol 2005; 18: 605 A.

48. Velazquez EF, Melamed J, Barreto JE et al. Sarcomatoid carcinoma of the penis: a clinicopathologic study of 15 cases. Am J Surg Pathol 2005; 29: 1152–8.

49. Cubilla AL, Ayala TM, Barreto JE et al. Surface adenosquamous carcinoma of the penis. A report of 3 cases. Am J Surg Pathol 1996; 20: 156–60.

50. Layfield LJ, Liu K. Mucoepidermoid carcinoma arising in the glans penis. Arch Pathol Lab Med 2000; 124: 148–51.

51. Lowenstein LW. Carcinoma-like condylomata acuminata of the penis. Med Clin North Am 1939; 23: 789–95.

52. Cubilla AL, Velazquez EF, Young RH. Pseudohyperplastic squamous cell carcinoma of the penis associated with lichen sclerosus. An extremely well-differentiated, nonverruciform neoplasm that preferentially affects the foreskin and is frequently misdiagnosed: a report of 10 cases of a distinctive clinicopathologic entity. Am J Surg Pathol 2004; 28: 895–900.

53. Aird I, Johnson HD, Lennox B et al. Epithelioma cuniculatum: a variety of squamous carcinoma peculiar to the foot. Br J Surg 1954; 42: 245–50.

54. Barreto JE, Velazquez EF, Ayala E et al. Carcinoma cuniculatum: a distinctive variant of penile squamous cell carcinoma. Report of 7 cases. Am J Surg Pathol 2006: in press.

55. Liegl B, Regauer S. Penile clear cell carcinoma: a report of 5 cases of a distinct entity. Am J Surg Pathol 2004; 28: 1513–17.

56. Caballero C, Cubilla AL, Barreto J et al. Factores patologicos relacionados con metastasis inguinal en carcinoma epidermoide del glande peneal. Patología (Spain) 1991; 24: 1137–41.

57. Villavicencio H, Rubio-Briones J, Regalado R et al. Grade, local stage and growth pattern as prognostic factors in carcinoma of the penis. Eur Urol 1997; 32: 442–7.

58. Slaton JW, Morgenstern N, Levy DA et al. Tumor stage, vascular invasion and the percentage of poorly differentiated cancer: independent prognosticators for inguinal node metastasis in penile squamous cancer. J Urol 2001; 165: 1138–42.

59. Adeyoyu AB, Thornhill J, Corr J et al. Prognostic factors in squamous cell carcinoma of the penis and implications for management. Br J Urol 1997; 80: 937–9.

60. Rubio-Briones J, Villavicencio H, Regalado R et al. Squamous cell carcinoma of the penis: treatment protocol according to our 14 years experience. Arch Esp Urol 1997; 50: 473–80.

61. Cubilla AL, Velazquez EF, Barreto JE et al. The penis. In: Mills SEPA, ed. Sternberg's Diagnostic Surgical Pathology, 4th edn. Philadelphia PA: Lippincott Williams & Wilkins; 2004.

62. Soria JC, Fizazi K, Piron D et al. Squamous cell carcinoma of the penis: multivariate analysis of prognostic factors and natural history in monocentric study with a conservative policy. Ann Oncol 1997; 8: 1089–98.

63. Fraley EE, Zhang Z, Manivel C et al. The role of inguinal lymphadenectomy and significance of histological differentiation in treatment of carcinoma of the penis. J Urol 1989; 142: 1478–82.

64. Cubilla AL, Chaux A, Torres J et al. Intuitive vs electronic quantification of proportions of grades in squamous cell carcinoma of the penis. Mod Pathol 2005; 18: 135 A.

65. Cubilla AL, Chaux A, Pfannl, et al. Any proportion of histologic grade 3 is related to metastasis in SCC of the penis. Mod Pathol 18; 135 A.

66. Velazquez EF, Soskin A, Bock A et al. Urethral epithelial abnormalities associated with invasive squamous cell carcinoma of the penis. Mod Pathol 2005; 18: 917–23.

67. Huvos A, Grabstald H. Urethral meatal and perimeatal tumors in young men: a clinicopathologic and electronmicroscopic study. J Urol 1973; 10: 688–92.

68. Alonso E, Marostica A, Roma S et al. Low grade papillary transitional cell carcinoma of the distal urethra with focal squamous differentiation and association with human papilloma virus types 6–11. Arch Esp Urol 1997; 50: 875–8.

69. Ayra M, Brown RW, Hayne D et al. Primary anterior urethral transitional cell carcinoma: a rare tumor. Surg Oncol 2001; 27: 607–8.

70. Bans LL, Eble JN, Lingeman JE et al. Transitional cell carcinoma of fossa navicularis of the male urethra. J Urol 1983; 120: 1055–6.

71. Cupp MR, Malek RS, Goellner JS et al. Detection of human papillomavirus DNA in primary squamous cell carcinoma of the male urethra. J Urol 1996; 48: 551–5.

72. Dalbagni G, Zhang ZF, Lacombe I et al. Male urethral carcinoma: analysis of treatment outcome. Urology 1999; 53: 1126–32.

73. Cubilla AL, Reuter V, Velazquez EF et al. Histologic classification of penile carcinoma and its relation to outcome in 61 patients with primary resection. Int J Surg Pathol 2001; 9: 111–20.

74. Emerson RE, Ulbright TM, Eble JN et al. Predicting cancer progression in patients with penile squamous cell carcinomas: the importance of depth of invasion and vascular invasion. Mod Pathol 2001; 14: 963–8.

75. Horenblas S, van Tinteren H. Squamous cell carcinoma of the penis. IV. Prognostic factors of survival: analysis of tumor, nodes and metastasis classification system. J Urol 1994; 151: 1239–43.

76. Velazquez EF, Zanotti M, Acevedo M et al. Anatomical levels of invasion and tumor thickness in invasive penile squamous cell carcinoma of the glans. A proposal of modification of the TNM system. Mod Pathol 2006; 19: 167A.

77. Cubilla AL, Chaux A, Zanotti M et al. Histologic grade is more important than tumor thickness as predictor of nodal metastasis in squamous cell carcinoma of the penis invading 5–10 mm. Mod Pathol 2006; 19: 134A.

78. Lutterbach J, Pagestecher A, Weyerbrock A et al. Early stage penile carcinoma metastasizing to brain: case report and literature review. Urology 2005; 66: 432.

79. Cubilla AL, Piris A, Pfannl R et al. Anatomical levels: important landmarks in penectomy specimens: a detailed anatomic and histologic study based on examination of 44 cases. Am J Surg Pathol 2001; 25: 1091–4.

80. Velazquez EF, Soskin A, Bock A et al. Positive resection margins in partial penectomies: sites of involvement and proposal of local routes of spread of penile squamous cell carcinoma. Am J Surg Pathol 2004; 28: 384–9.

81. Mikuz G, Winstanley AM, Sculman CC et al. Handling and pathology reporting of circumcision and penectomy specimens. Eur Urol 2004; 46: 434–9.

82. Ficarra V, Martignoni G, Maffei N et al. Predictive pathological factors of lymph node involvement in the squamous cell carcinoma of the penis. Int Urol Nephrol 2002; 34: 245–50.

83. Lopez AA, Hidalgo GS, Kowalski LP et al. Prognostic factors in carcinoma of the penis: multivariate analysis of 145 patients treated with amputation and lymphadenectomy. J Urol 1996; 156: 1637–42.

84. Maiche AG, Pyrhonen S, Karkinen M. Histological grading of squamous cell carcinoma of the penis: a new scoring system. Br J Urol 1991; 67: 522–6.

85. McDougal WS. Carcinoma of the penis: improved survival by early regional lymphadenectomy based on the histologic grade and depth of invasion of the primary lesion. J Urol 1995; 154: 1364–6.

86. Solsona E, Iborra I, Rubio J et al. Prospective validation of the association of local tumor stage and grade as a predictive factor for occult lymph node micrometastasis in patients with penile carcinoma and clinically negative inguinal lymph nodes. J Urol 2001; 165: 1506–9.

87. Velazquez EF, Barreto JE, Rodriguez I et al. Limitations in the interpretation of biopsies in patients with penile squamous cell carcinoma. Int J Surg Pathol 2004; 12: 139–46.

88. Cubilla AL, Caballero C, Piris A et al. Prognostic Index (PI): a novel method to predict mortality in squamous cell carcinoma of the penis. Lab Inv 2000; 80: 97 A.

89. Cubilla AL, Velazquez EF, Chaux A et al. Prognostic Index in 110 invasive squamous cell carcinoma of the penis. A useful guide for the management of inguinal lymph node dissections. Mod Pathol 2006; 19: 134 A.

90. Hadway P, Kommu SS, Watkin NA. Expression of Ki67 in squamous cell carcinoma of the penis. BJU 2005; 96: 1146–7.

91. Hall MC, Sanders JS, Viutch F et al. Deoxyribonucleic acid flow cytometry and traditional pathologic variables in invasive penile carcinoma: assessment of prognostic significance. Urology 1998; 52: 111–16.

92. Martins AC, Farias SM, Cologna AJ et al. Inmunoexpression of p53 protein and proliferating cell nuclear antigen in penile carcinoma. J Urol 2002; 167: 89–92.

93. Lopez A, Bezerra AL, Pinto CA et al. P53 as a new prognostic factor for lymph node metastasis in penile carcinoma: analysis of 82 patients treated with amputation and bilateral lymphadenectomy. J Urol 2002; 168: 81–6.

94. Algaba F, Trias I, Santinelli A et al. Tp53 in urologic tumors. Anal Quant Cytol Histol 2003; 25: 123–30.

95. Ono Y, Osawa M, Tamura Y et al. Tumor-associated tissue eosinophilia of penile cancer. Int J Urol 2002; 9: 82–7.

96. Riveros M, Garcia R, Cabanas R. Lymphadenography of the dorsal lymphatics of the penis. Technique and results. Cancer 1967; 20: 2026–31.

97. Cabanas RM. An approach for the treatment of penile carcinoma. Cancer 1977; 39: 456–66.

98. Horenblas S. Tanis PJ, Lont AP et al. Dynamic sentinel node biopsy for penile cancer: reliability of a staging technique. J Urol 2002; 168: 76–80.

99. Cubilla AL,Velazquez EF, Codas R et al. Autopsy findings in 14 patients with penile squamous cell carcinoma. Mod Path 2004; 17: 5A.

100. Greene FL, Page D, Fritz A et al, eds. AJCC Cancer Staging Manual, 6th edn. Springer, 2002.

101. Aynaud O, Ionesco M, Barrasso R. Penile intraepithelial neoplasia. Specific clinical features correlate with histologic and virologic findings. Cancer 1994; 74: 1762–7.

102. Aynaud O, Asselain B, Bergeron C et al. Intraepithelial carcinoma and invasive carcinoma of vulva, vagina and penis in Ile-de-France. Ann Dermatol Venereol 2000; 127: 479–83.

103. Cubilla AL, Velazquez EF, Young RH. Epithelial lesions associated with invasive penile squamous cell carcinoma: a pathological study of 288 cases. Int J Surg Pathol 2004; 12: 351–64.

104. Nasca MR, Innocenzi D, Micali G. Penile cancer among patients with genital lichen sclerosus. J Am Acad Dermatol 1999; 41: 911–14.

105. Micali G, Nasca MR, Innoscenzi D. Lichen sclerosus of the glans is significantly associated with penile carcinoma. Sex Transm Infect 2001; 77: 226.

Section 8

Handling of surgical specimens

Gregor Mikuz

The clinical presentation of penis cancer may range from small erythematous lesions to ulcers or verrucous exophytic growing tumors. Small lesions of the foreskin can be treated by circumcision. Carcinomas involving the glans and the shaft are best managed by partial penectomy; bulky tumors require a total penectomy with perineal urethrotomy, with or without local lymphadenectomy.[1] Another approach is the use of sentinel node for the staging of penis cancer.[2]

The penis is composed of the glans, balanopreputial (coronal) sulcus, and the foreskin. The central portion is formed by the shaft and the posterior end is the root of the penis. From outer to inner, the cross-section shows the following structures: skin and the attached muscle, fascia penis superficialis and profunda (Buck's fascia), tunica albuginea, corpora cavernosa, and the urethra which is surrounded by the corpus spongiosum with its own tunica albuginea. The two arteries superficiales penis and the veins are located between the fascia penis superficialis and the tunica albuginea. The two arteries profundae penis are in the middle of the right and left corpus cavernosus. The lymphatic channels drain to the deep and superficial inguinal lymph nodes.

Circumcision

The epithelial margins of the specimen have to be inked. The four corners of the foreskin should be pinned on a sheet of cork and then the whole specimen fixed in formalin. After fixation the number and size of lesions are recorded and their gross pathology described. For histology serial perpendicular sections are performed. The number of sections depends on the dimension of the lesion. Each epithelial margin should be sampled.

Total or partial penectomy

The anatomic location of any lesion should be identified and its size measured. Then a shave section of the shaft (surgical margin) is taken. The specimen is mostly large and must be divided in two parts. Especially in frozen sections the urethra and the periurethral corpus spongiosum should be separately examined because this is the region of invasive tumor spread.[3] After the foreskin has been removed and, if necessary, pinned on a table or cork, the penis should be longitudinally bisected using the urethra as a guide. The size and depth of any tumor should be documented. Sections of the tumor, foreskin, transverse sections through the shaft and longitudinal glans sections are required for histology.

Lymphadenectomy

Lymph nodes without overt metastasis greater than 5 mm are cut through the hilus in 2 mm thick parallel slices. Lymph nodes smaller than 5 mm along the longitudinal axis are entirely processed. When the lymph node contains an evident metastasis 1–2 sections are usually enough.

Sentinel lymph nodes

These are often detected with lymphoscintigraphy[1] and are labeled with radioactive colloid. Negative lymph nodes are entirely processed (steps of 250 μm). Every second section could be used for cytokeratin immunocytochemistry.

Frozen sections

These can be used for the evaluation of the resection margins and of the sentinel lymph node.

Resection margins

Usually the tumor spreads in the urethra, periurethral vessels, and soft tissue, which should thus be frozen for histologic evaluation. In circumcision specimens the entire circumference and thickness of the surgical margin should be frozen and evaluated.[3] To avoid unnecessary sections the surgeon can mark the area of concern with a suture.

(Sentinel) lymph nodes

When a frozen section is requested the lymph node should be bisected and one section (not more!) from each cut surface should be made. Then both halves are embedded and the first slides H&E stained.

Pathology reporting of surgical specimens (circumcision and penectomy)

The pathology report should provide useful information for the therapy and prognosis of the penile lesions. It should thus include

the histologic diagnosis and all factors which have a predictive value:[3] histologic type, tumor grade, and the depth of invasion (pT/stage).

References

1.   Cabanas RM. An approach for the treatment of penile carcinoma. Cancer 1977; 39: 456–66.

2.   Kroon BK, Horenblas S, Nieweg OE. Contemporary management of penile squamous cell carcinoma. J Surg Oncol 2005; 89: 43–50.

3.   Mikuz G, Winstanley AM, Schulman CC et al. Handling and pathology reporting of circumcision and penectomy specimens. Eur Urol 2004; 46: 434–9.

Section 9

Pathology of tumors of the renal pelvis and ureter, and the urethra

Antonio Lopez-Beltran, Rodolfo Montironi, Alfredo Vidal-Jimenez, and Liang Cheng

The renal pelvis and ureter

Tumors arising in the renal pelvis, the ureter, and the urethra are morphologically similar to those in the bladder[1–6] (Table 9.1). The incidence of these tumors ranges from 0.7 to 1.1 per 100 000 and there is a male to female ratio of 1.7 to 1 with an increasing incidence in females.[7] Tumors of the ureter and renal pelvis account for 8% of all urinary tract neoplasms and are more common in older patients (mean 70 years).[8,9] More than 90% are urothelial carcinomas.[1,10,11] Hematuria and flank pain are the chief presenting symptoms.[12–20]

Benign epithelial tumors

In this location, most benign epithelial tumors are urothelial papillomas, inverted papillomas, villous adenomas, and squamous papillomas.[21–24] Most lesions are incidental findings and show similar histology to bladder cases.[21–24] Synchronous inverted papilloma of the urinary bladder and the renal pelvis may occur.[24] Benign epithelial tumors are rare in the upper urinary tract.[18]

Urothelial carcinoma

Carcinomas arising in the renal pelvis and calyces are twice as common as those of the ureter.[25,26] Multifocality is frequent as it is the association with a bladder neoplasm.[18,25,27] Bilateral synchronous or metachronous ureteral and renal pelvic carcinomas may occur.[11,14–16]

Etiologic and predisposing factors additional to those for bladder malignancy include phenacetin abuse, papillary necrosis, Balkan nephropathy, thorium-containing radiologic contrast material, urinary tract infections, or nephrolithisis.[9,25] Some tumors of the ureter are associated with hereditary non-polyposis colon cancer syndrome (Lynch syndrome).[27] Grossly, tumors may be papillary, polypoid, nodular, ulcerative, or infiltrative (Figure 9.1). Some tumors distend the entire pelvis while others ulcerate and infiltrate, causing thickening of the wall.[10,12,15,19,20,25] A high-grade tumor may appear as an ill-defined mass that involves the renal parenchyma, mimicking a primary renal cell carcinoma.[25] Hydronephrosis and stones may be present in renal pelvic tumors while hydroureter and/or stricture may accompany ureteral neoplasms[18] (Figure 9.2). At histology, renal pelvis and bladder urothelial malignancies mirror bladder urothelial neoplasia and, therefore, occur with similar histology including papillary non-invasive or invasive tumors, carcinoma in situ and solid invasive carcinoma.[1–3,11,14,15,20] The entire morphologic spectrum of urothelial carcinoma and its variants may be seen[3,11] and tumor types include those showing squamous and glandular differentiation, inverted growth, or different morphologic variants (nested, microcystic, micropapillary, clear cell, and plasmacytoid), and poorly differentiated or undifferentiated carcinoma (lymphoepithelioma-like, sarcomatoid, and giant cell)[3,4,11,20,28–42] (Figure 9.3). Sarcomatoid carcinoma is rare in the pelvis and ureter, has a poor prognosis, and shows either homologous or heterologous stromal elements[30,36] (Figure 9.4). Rare cases of choriocarcinoma reported in this location are viewed at this time as high-grade urothelial carcinoma with trophoblastic differentiation.[3,43] Some urothelial carcinomas in this location display alfa-fetoprotein or cyclooxygenase-2 expression at immunohistochemistry.[42,44] Synchronous renal cell carcinoma and urothelial cell carcinoma may coexist.

Urothelial tumors should be graded following the proposal for the bladder urothelial tumors made by the World Health Organization (WHO) in 2004[1,12,14,19,20,45] or, until validated, both the WHO, 1973 and WHO, 2004 can be stated in the final pathology report.[1] The existence of the papillary urothelial neoplasia of low malignant potential in the upper urinary tract has been recently challenged.[1,12,14,19,20,45] There is a separate Tumor Node and Metastases (TNM) staging system for tumors of the renal pelvis and ureter according to the AJCC/TNM, 2002 revision (Table 9.2).[46]

The most important prognostic factor is tumor stage.[12,46] In evaluating these specimens, it is important to avoid overstaging as pT3 tumors that invade the muscularis (pT2) but show extension into renal tubules in a pagetoid or intramucosal pattern.[8] Survival for patients with pTa/pTis lesions is essentially 100% but declines up to 75% in patients with pT2. Survival for patients with pT3 and pT4 tumors, tumors with nodal involvement, and residual tumor after surgery is poor.[18,25] Other prognostic factors include patient age, type of treatment, and presence and severity of concurrent urothelial neoplasia.[12,25] The characteristics of invading neoplastic nests (infiltrative vs nodular or trabecular), vascular invasion, and tumor necrosis could be of prognostic significance.[12,19,20] It has been suggested that Ki-67 overexpression might be of prognostic value and that ErbB2 expression could be a predictor of disease progression and disease-related survival in upper urothelial carcinoma.[47,48]

Squamous cell carcinoma

Squamous cell carcinoma is very rare but may occur in the renal pelvis where it follows in frequency to urothelial carcinoma.[25,32,40,49]

Table 9.1 WHO histologic classification of tumors of renal pelvis and ureter

Epithelial tumors
Benign
Urothelial papilloma
Inverted papilloma
Squamous cell papilloma
Villous adenoma
Malignant
Urothelial carcinoma
   nested
   microcystic
   inverted
   micropapillary
   clear cell
   with squamous differentiation
   with glandular differentiation
   lymphoepithelioma-like
   sarcomatoid
   giant cell
Squamous cell carcinoma
Adenocarcinoma
Small cell carcinoma
Undifferentiated carcinoma

Non-epithelial tumors
Benign
Fibroepithelial polyp
Leiomyoma
   fibrous-histiocytoma
Neurofibroma
Hemangioma
Lipoma
Hibernoma
Malignant
Leiomyosarcoma
   Rhabdomyosarcoma
Fibrosarcoma
Angiosarcoma
   Osteosarcoma
Malignant schwannoma

Miscellaneous
   Pheochromocytoma
   Carcinoid
Lymphoma
Plasmacytoma
Wilms' tumor
Choriocarcinoma
Malignant melanoma

Figure 9.1
Papillary urothelial carcinoma of the renal pelvis.
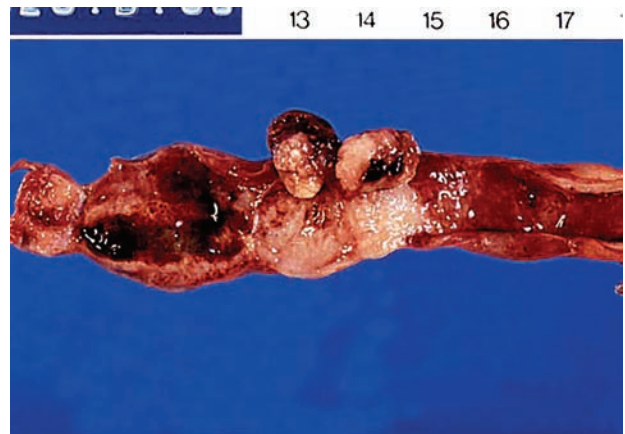
Figure 9.2
Papillary urothelial carcinoma of the ureter.

signet-ring cell).[33,39,51] Glandular (intestinal) metaplasia, nephrolithiasis, and repeated infections are predisposing factors. Most adenocarcinomas are high-grade and are widely invasive at presentation.[51,52]

Squamous differentiation in an otherwise urothelial carcinoma is seen in about 40% of cases of the renal pelvis.[2] Pure squamous cell carcinomas are usually high-grade and high-stage tumors and frequently invade the kidney; they usually occur in the background of nephrolithiasis, chronic inflammation, or in association with squamous metaplasia.[25,49] Some squamous cell carcinomas may present with hypercalcemia, but they are unrelated to Epstein–Barr virus infection.[50] Survival at 5 years' follow-up is poor.[25,49]

Adenocarcinoma

Pure adenocarcinomas of the renal pelvis and ureters are rare, showing similar morphologic types as in the bladder (enteric, mucinous, or

Soft tissue tumors of renal pelvis and ureter

Rare examples of non-epithelial tumors and tumor-like conditions arising in the renal pelvis and/or ureter have been described including leiomyoma, neurofibroma, fibrous-histiocytoma, hemangioma, lipoma, and hibernoma glomus tumor.[10,53–59] Fibroepithelial polyp is a tumor-like condition growing as an exophytic intraluminal mass of vascular connective and inflammatory cells covered by normal urothelium; rare cases may have a prominent peudosarcomatous stroma.[60] Malignant soft tissue tumors include leiomyosarcoma and less frequently rhabdomyosarcoma, osteosarcoma, fibrosarcoma, angiosarcoma, malignant schwannoma, and Ewing sarcoma;
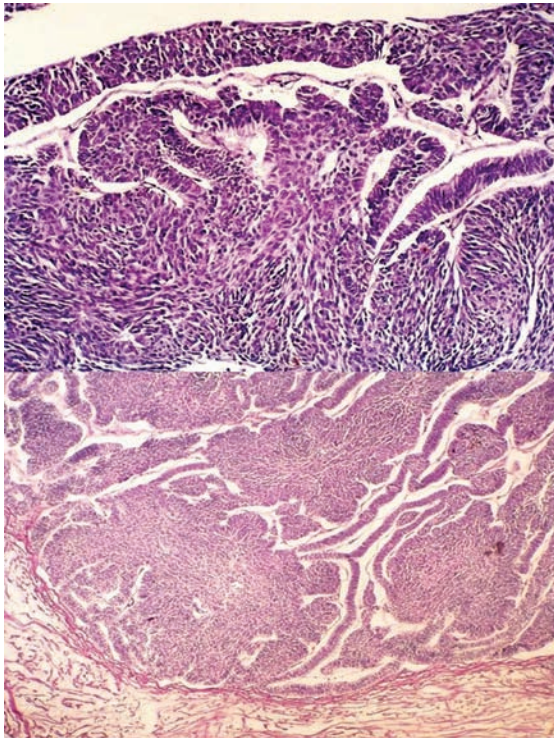
Figure 9.3
Surface (above) and deep (below) aspects of a urothelial carcinoma of the renal pelvis with inverted growth.
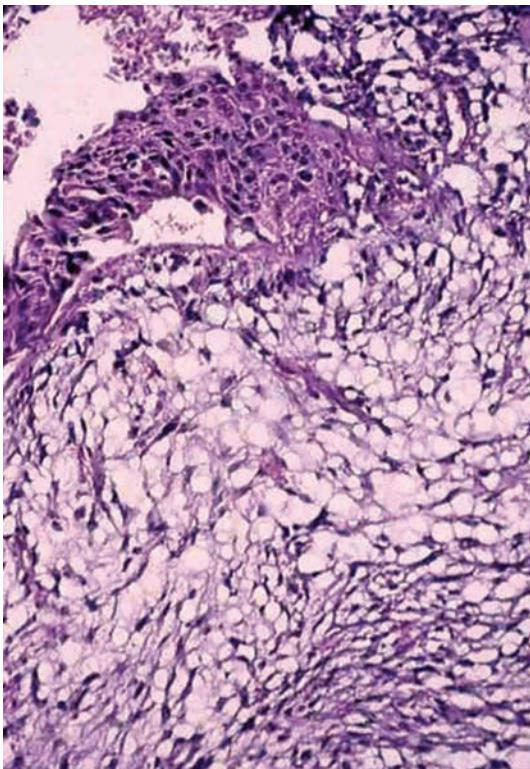
Figure 9.4
Sarcomatoid urothelial carcinoma primary in the renal pelvis with myxoid appearance.

Table 9.2 TNM classification of tumors of the renal pelvis and ureter

T – Primary Tumor

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades muscularis
T3	(Renal pelvis) Tumor invades beyond muscularis into peripelvic fat or renal parenchyma (Ureter) Tumor invades beyond muscularis into periureteric fat
T4	Tumor invades adjacent organs or through the kidney into perinephric fat

N – Regional Lymph Nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node 2 cm or less in greatest dimension
N2	Metastasis in a single lymph node more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, none more than 5 cm in greatest dimension
N3	Metastasis in a lymph node more than 5 cm in greatest dimension

M – Distant Metastasis

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

gastrointestinal stromal tumor-like lesions as well as myofibroblastic proliferations may occur.[54–60]

Other tumors

Few cases of ureteric pheochromocytoma have been reported.[10,54–60] Pelvic and ureteric carcinoid is similarly rare and must be differentiated from metastatic disease. Small cell carcinoma of the renal pelvis is a rarity observed in elderly patients.[10,40] These aggressive tumors usually contain foci of urothelial carcinoma and have a typical neuroendocrine immunohistochemical profile. Renal pelvic and ureteric lymphomas are usually associated with systemic disease, while localized pelvic plasmacytoma has been reported.[61] Wilms tumor confined to the renal pelvis or extending into the ureter and cases of malignant melanoma of the renal pelvis may be seen rarely in the literature.[10,53] A curious case of tumor-like lesion of the renal pelvis composed of Liesegang rings has been reported.[62]

The urethra

This category includes epithelial and non-epithelial neoplasms of the male and female urethra, from the urinary bladder to the urethral meatus, and tumors arising in the accessory glands (Cowper and Littre glands as well as Skene glands in the female) (Table 9.3).[26] Epithelial tumors of the urethra are rare and three to four times more common in women than in men.[26] Urethral carcinomas occurring in men are

Table 9.3 Histologic classification of the tumors of the urethra

Epithelial tumors
Benign
Squamous papilloma
Villous adenoma
Urothelial papilloma including inverted papilloma
Malignant
Primary
   squamous cell carcinoma
   urothelial carcinoma
   adenocarcinoma
     clear cell carcinoma
     non-clear cell carcinoma
      enteric
      colloid (mucinous) carcinoma
      signet-ring cell carcinoma
      adenocarcinoma, not otherwise specified (NOS)
   adenosquamous carcinoma
   neuroendocrine carcinoma
   undifferentiated carcinoma
Secondary

Non-epithelial tumors
Benign
Leiomyoma
Hemangioma
Glomangiomyoma
Malignant
Malignant melanoma
Non-Hodgkin-lymphoma
Plasmocytoma

Tumor-like lesions
Fibroepithelial polyp
Prostatic polyp
Carcuncle
Condyloma accuminatum
Nephrogenic adenoma (metaplasia)

Tumors of accessory glands
Malignant
Carcinoma of Skenes, Littres, and Cowpers glands

strikingly different in clinical and pathologic features when compared to tumors in women. This difference seems to be attributable to the distinct differences in the anatomy and histology of the urethra in the two sexes.[26] Benign epithelial tumors are exquisitely rare in the urethra of either sex. Congenital diverticulum, as well as acquired strictures of the female urethra, contribute to the female preponderance of carcinomas. Columnar and mucinous adenocarcinomas are thought to arise from glandular metaplasia, whereas cribriform adenocarcinoma that shows PSA staining seems to originate from Skene glands.[26]

Benign epithelial tumors of the urethra

Tumors occurring in males are similar to those in the female urethra. Some reports on squamous papilloma, villous adenoma, and urothelial papilloma of the urethra are available but overall are rare.[26]

Inverted papilloma has also been reported in the urethra.[63] The histologic features are identical to neoplasms described in the urinary bladder and other sites. Villous adenoma of the urethra has been shown to occur associated with tubulo-villous adenoma and adenocarcinoma of the rectum.[64]

Carcinoma of the urethra

Tumors involving the distal urethra and meatus are most common and appear as exophytic nodular, infiltrative, or papillary lesions with frequent ulceration.[65–70] Tumors involving the proximal urethra that are urothelial exhibit macroscopic diversity with cases showing papillary growth, carcinoma in situ (erythematous or white plaque-like), or the nodular/infiltrative growth of invasive carcinoma[26,65–69] (Figure 9.5). Adenocarcinomas are often large infiltrative or expansile neoplasms which may have an exophytic surface.[70–75] They can be mucinous, gelatinous, or cystic. These tumors may occur within urethral diverticulum[26,70–75] (Figure 9.6). Other tumors may occur in the penile urethra, bulbomembranous urethra, or the prostatic urethra, which often determines the gross and histologic appearance. These tumors may grow as ulcerative, nodular, papillary, cauliflower-like, or ill-defined lesions.[26] At histology, there are some differences between female and male urethral carcinomas, mainly because of the different anatomic location. Distal urethral and meatus tumors are squamous cell carcinomas (70%), and tumors of the proximal urethra are urothelial carcinomas (20%) or adenocarcinomas (10%).[65–75] Squamous cell carcinomas of the urethra span the range from well-differentiated (including the rare verrucous carcinoma), to moderately differentiated (most common), to poorly differentiated.[65–75]
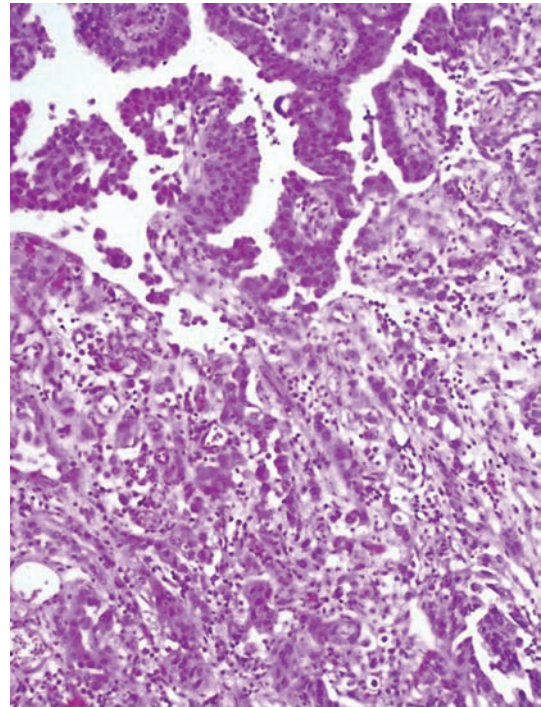
Figure 9.5
Urothelial carcinoma of the urethra showing papillary and invasive components, arising in a diverticulum.
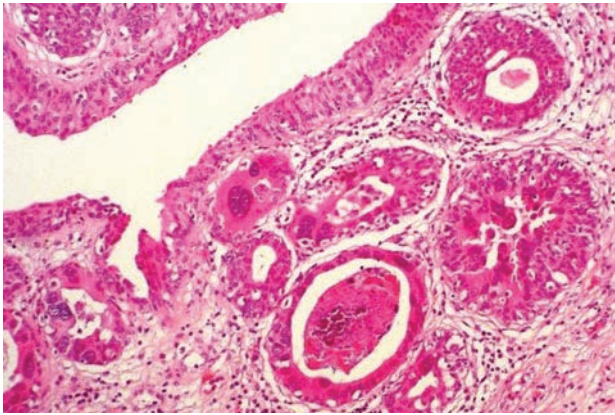
Figure 9.6
Urothelial carcinoma in situ extending through periurethral ducts.

Urothelial neoplasms may be non-invasive, papillary low-grade or high-grade carcinomas, carcinoma in situ, or invasive urothelial carcinoma.[66,69] Carcinoma in situ may involve suburethral glands, focally or extensively, a fact that should not be mistaken as invasion. Deeply invasive carcinomas are high grade, with or without papillary component, and characterized by irregular nests, sheets, or cords of cells accompanied by a desmoplastic and/or inflammatory response. Tumors may exhibit squamous or glandular differentiation or unusual morphologic variations (nested, microcystic, micropapillary, clear cell, or plasmacytoid).[3] A small cell or sarcomatoid carcinoma component is rarely seen.[72] In the penile and bulbomembranous urethra about 75% of carcinomas are squamous cell carcinoma followed by urothelial carcinomas (usually prostatic urethra and less commonly bulbomembranous and penile urethra), adenocarcinomas (usually bulbomembranous urethra), or undifferentiated carcinoma.[65–75] Squamous cell carcinomas are similar in histology to invasive squamous cell carcinomas at other sites.

Urothelial carcinoma may involve the prostatic urethra, exhibiting the same grade and histologic spectrum described in the female urethra. It may be synchronous or metachronous to bladder neoplasia. Features unique to prostatic urethral urothelial cancers are the frequent proclivity of high-grade tumors to extend into the prostatic ducts and acini in a pagetoid fashion.[66]

Adenocarcinoma of the female urethra may be seen in the form of two patterns, clear cell adenocarcinoma (approximately 40%) and non-clear cell adenocarcinoma (approximately 60%), the latter frequently exhibiting similar patterns as in other portions of the urinary tract (enteric, mucinous, signet-ring cell, or adenocarcinoma not otherwise specified). Clear cell adenocarcinomas are usually characterized by pattern heterogeneity within the same neoplasm and show solid, tubular, tubulocystic or papillary patterns (Figure 9.7). The cytologic features vary from low-grade (resembling nephrogenic adenoma focally) to high-grade (more frequently). Necrosis, mitotic activity, and extensive infiltrative growth are commonly observed. The relationship to nephrogenic adenoma remains uncertain.[65–75]

Urothelial neoplasms are graded as outlined in the urinary bladder.[26,45] Adenocarcinomas and squamous cell carcinomas are usually graded following similar carcinomas in other organs – well-, moderately, and poorly differentiated carcinomas using the classic criteria of degree of differentiation.[26] Bulbourethral gland carcinomas may show a mucinous, papillary, adenoid cystic, acinar, or
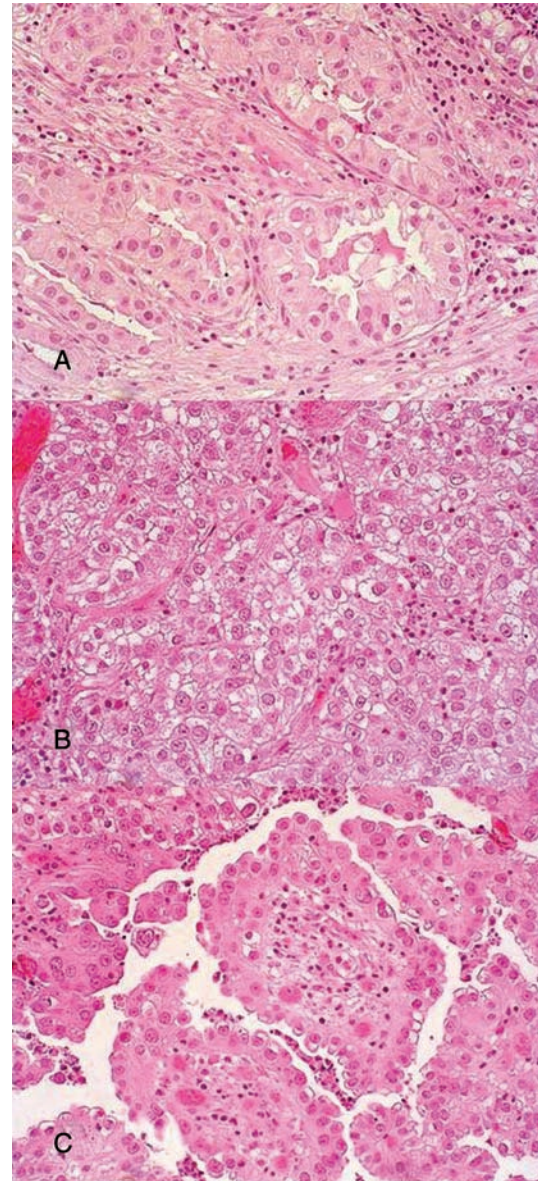
Figure 9.7
Clear cell adenocarcinoma of the urethra showing (A) tubular, (B) solid, and (C) papillary pattern.

tubular architecture.[26] Female periurethral gland adenocarcinomas are clear cell or mucinous and often show prostate specific antigen immunoexpression.

There is a separate Tumor Node and Metastases (TNM) staging system for tumors of the urethra (Table 9.4).[46] The overall prognosis is relatively poor.[26] Tumor stage and location are important prognostic factors.[65–75] In females and males, proximal tumors have better overall survival than distal tumors (51% for proximal versus 6% for distal in females, and 50% for proximal and 20% 5-year survival for distal tumors in males).[26] In both sexes, high pT tumor stage and the presence of lymph node metastasis are adverse prognostic parameters.[26] A number of tumor-like conditions entering the differential diagnosis of urethral carcinoma include nephrogenic metaplasia (adenoma), fibroepithelial and prostatic polyps, condyloma acuminatum, and caruncle.[69]

Table 9.4 TNM classification of tumors of the urethra

T – Primary Tumor

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor

Urethra (male and female)

Ta	Non-invasive papillary, polypoid, or verrucous carcinoma
Tis	Carcinoma in situ
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades any of the following: corpus spongiosum, prostate, periurethral muscle
T3	Tumor invades any of the following: corpus cavernosum, beyond prostatic capsule, anterior vagina, bladder neck
T4	Tumor invades other adjacent organs

Urothelial carcinoma of prostate (prostatic urethra)

Tis pu	Carcinoma in situ, involvement of prostatic urethra
Tis pd	Carcinoma in situ, involvement of prostatic ducts
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades any of the following: prostatic stroma, corpus spongiosum, periurethral muscle
T3	Tumor invades any of the following: corpus cavernosum, beyond prostatic capsule, bladder neck (extraprostatic extension)
T4	Tumor invades other adjacent organs (invasion of bladder)

N – Regional Lymph Nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node 2 cm or less in greatest dimension
N2	Metastasis in a single lymph node more than 2 cm in greatest dimension, or multiple lymph nodes

M – Distant Metastasis

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Non-epithelial tumors of the urethra

Rare examples of non-epithelial tumors arising in the urethra have been described. Benign tumors include leimyoma with similar morphology and immunoprofile as in other organs; in female patients leiomyoma may show expression of estrogen receptors.[76–79] Leiomyoma may occur as a part of diffuse leiomyomatosis syndrome (esophageal and rectal leiomyoma). Hemangioma and plasmacytoma have also been described.[76–79]

Malignant melanoma has also been described in the male and female urethra with some cases of amelanotic melanoma mimicking urethral carcinoma.[80] Primary non-Hodgkin lymphoma has also being described.[76,77]

Molecular pathology

Urothelial carcinomas of the renal pelvis, ureter, and urinary bladder show molecular similarities to bladder carcinoma, but microsatellite instability (MSI) is more common in upper urinary tract cancers.[81–85]

Deletions on chromosome 9p and 9q occur in 50–75% of all patients and frequent deletions at 17p in addition to p53 mutations are seen in advanced invasive tumors. Between 20 and 30% of all upper urinary tract cancers demonstrate MSI and loss of the mismatch repair proteins MSH2, MLH1, or MSH6.[81] Mutations in the sequences of TGFß-RII, Bax, MSH3, and MSH6 genes are found in 20–33% of cases with MSI, indicating a molecular pathway of carcinogenesis that is similar to some mismatch repair-deficient colorectal cancers.[26] Tumors with MSI have different clinical and histologic features including low tumor stage and grade, papillary growth, and a higher prevalence in female patients; some of these tumors exhibit an inverted growth pattern.[81–85]

Squamous cell carcinoma of the urethra is associated with human papillomavirus (HPV) infection in female and male patients.[84,85] High-risk HPV 16 or 18 may be detected in up to 60% of urethral carcinomas in women. In men, about 30% of squamous cell carcinomas tested positive for HPV16; tumors in the bulbar urethra are usually negative. Some HPV16-positive tumors might have a more favorable prognosis.[26] Low-risk HPV infection plays a crucial role in the etiology of condyloma acuminatum of the urethra. The association of urothelial carcinoma with HPV, both in the urethra and the urinary bladder, remains controversial, but the variable reported incidence might be related to geographic or demographic issues.[86]

References

1. Lopez-Beltran A, Montironi R. Non-invasive urothelial neoplasms: according to the most recent WHO classification. Eur Urol 2004; 46: 170–6.
2. Lopez-Beltran A, Requena MJ, Alvarez-Kindelan J et al. Squamous differentiation in primary urothelial carcinoma of the urinary tract as seen by Mac387 immunohistochemistry. J Clin Pathol 2006.
3. Lopez-Beltran A, Cheng L. Histologic variants of urothelial carcinoma: differential diagnosis and clinical implications. Hum Pathol 2006; 37: 1371–88.
4. Lopez-Beltran A, Sauter G, Gasser T et al. Urothelial tumors: infiltrating urothelial carcinoma. In: Eble JN, Sauter G, Epstein JI, Sesterhenn I, eds. World Health Organization Classification of Tumors. Pathology and Genetics of Tumors of the Urinary System and Male Genital Organs. Lyon, France: IARC Press; 2004.
5. Bostwick DG, Ramnani D, Cheng L. Diagnosis and grading of bladder cancer and associated lesions. Urol Clin North Am 1999; 26: 493–507.
6. Bostwick DG, Mikuz G. Urothelial papillary (exophytic) neoplasms. Virch Arch 2002; 441: 109–16.
7. Jemal A, Siegel R, Ward E et al. Cancer statistics 2006. CA Cancer J Clin 2006; 56;106–30.
8. Lopez-Beltran A, Bassi PF, Pavone-Macaluso M et al. Handling and pathology reporting of specimens with carcinoma of the urinary bladder, ureter, and renal pelvis. A joint proposal of the European Society of Uropathology and the Uropathology Working Group. Virch Arch 2004; 445: 103–10.
9. Brock KE, Gridley G, Brown LM et al. Dietary factors and cancers of the renal pelvis and ureter. Cancer Epidemiol Biomarkers Prev 2006; 15(5): 1051–3.
10. Busby JE, Brown GA, Tamboli P et al. Upper urinary tract tumors with nontransitional histology: a single-center experience. Urology 2006; 67(3): 518–23.
11. Perez-Montiel D, Wakely PE, Hes O et al. High-grade urothelial carcinoma of the renal pelvis: clinicopathologic study of 108 cases with emphasis on unusual morphologic variants. Mod Pathol 2006; 19(4): 494–503.
12. Langner C, Hutterer G, Chromecki T et al. pT classification, grade, and vascular invasion as prognostic indicators in urothelial carcinoma of the upper urinary tract. Mod Pathol 2006; 19(2): 272–9.

13. Holmang S, Johansson SL. Bilateral metachronous ureteral and renal pelvic carcinomas: incidence, clinical presentation, histopathology, treatment and outcome. J Urol 2006; 175(1): 69–72.

14. Holmang S, Johansson SL. Urothelial carcinoma of the upper urinary tract: comparison between the WHO/ISUP 1998 consensus classification and WHO 1999 classification system. Urology 2005; 66(2): 274–8.

15. Olgac S, Mazumdar M, Dalbagni G et al. Urothelial carcinoma of the renal pelvis: a clinicopathologic study of 130 cases. Am J Surg Pathol 2004; 28(12): 1545–52.

16. Holmang S, Johansson SL. Synchronous bilateral ureteral and renal pelvic carcinomas: incidence, etiology, treatment and outcome. Cancer 2004; 15; 101(4): 741–7.

17. Park S, Hong B, Kim CS et al. The impact of tumor location on prognosis of transitional cell carcinoma of the upper urinary tract. J Urol 2004; 171(2 Pt 1): 621–5.

18. Kirkali Z, Tuzel E. Transitional cell carcinoma of the ureter and renal pelvis. Crit Rev Oncol Hematol 2003; 47(2): 155–69.

19. Langner C, Hutterer G, Chromecki T et al. Tumor necrosis as prognostic indicator in transitional cell carcinoma of the upper urinary tract. J Urol 2006; 176(3): 910–13.

20. Langner C, Hutterer G, Chromecki T et al. Patterns of invasion and histological growth as prognostic indicators in urothelial carcinoma of the upper urinary tract. Virch Arch 2006; 448(5): 604–11.

21. Sung MT, Maclennan GT, Lopez-Beltran A et al. Natural history of urothelial inverted papilloma. Cancer 2006.

22. Sauter G. Inverted papilloma. In: Eble JN, Sauter G, Epstein JI, Sesterhenn I, eds. WHO Classification of Non-invasive Papillary Urothelial Tumors. In: World Health Organization Classification of Tumors. Pathology and Genetics of Tumors of the Urinary System and Male Genital Organs. Lyon, France: IARCC Press; 2004.

23. Cameron KM, Lupton CH. Inverted papilloma of the lower urinary tract. Br J Urol 1976; 48: 567–77.

24. Darras J, Inderadjaja N, Vossaert P. Synchronous inverted papilloma of bladder and renal pelvis. Urology 2005; 65(4): 798.

25. Delahunt B, Amin MB, Hofstädter F et al. Tumors of the renal pelvis and ureter. In: Eble JN, Sauter G, Epstein JI, Sesterhenn I, eds. World Health Organization Classification of Tumors. Pathology and Genetics of Tumors of the Urinary System and Male Genital Organs. Lyon, France: IARCC Press; 2004.

26. Hofstaedter F, Amin MB, Delahunt B et al. Tumors of the urethra. In: Eble JN, Sauter G, Epstein JI, Sesterhenn I, eds. World Health Organization Classification of Tumors. Pathology and Genetics of Tumors of the Urinary System and Male Genital Organs. Lyon, France: IARCC Press; 2004.

27. Bermejo JL, Eng C, Hemminki K. Cancer characteristics in Swedish families fulfilling criteria for hereditary nonpolyposis colorectal cancer. Gastroenterology 2005; 129(6): 1889–99.

28. Jones TD, Wang M, Eble JN et al. Molecular evidence supporting field effect in urothelial carcinogenesis. Clin Cancer Res 2005; 11: 6512–19.

29. Roig JM, Amerigo J, Velasco FJ et al. Lymphoepithelioma-like carcinoma of ureter. Histopathology 2001; 39: 106–7.

30. Lopez-Beltran A, Escudero AL, Cavazzana AO et al. Sarcomatoid transitional cell carcinoma of the renal pelvis. A report of five cases with clinical, pathological, immunohistochemical and DNA ploidy analysis. Pathol Res Pract 1996; 192: 1218–24.

31. Leroy X, Leteurtre E, De La Taille A et al. Microcystic transitional cell carcinoma: a report of 2 cases arising in the renal pelvis. Arch Pathol Lab Med 2002; 126: 859–61.

32. Kobayashi M, Hashimoto S, Hara Y et al. Squamous carcinoma with pseudosarcomatous stroma of the renal pelvis and ureter: a case report. Hinyokika Kiyo 1994; 40: 55–9.

33. Kotliar SN, Wood CG, Schaeffer AJ et al. Transitional cell carcinoma exhibiting clear cell features. A differential diagnosis for clear cell adenocarcinoma of the urinary tract. Arch Pathol Lab Med 1995; 119: 79–81.

34. Fukunaga M, Ushigome S. Lymphoepithelioma-like carcinoma of the renal pelvis: a case report with immunohistochemical analysis and in situ hybridization for the Epstein–Barr viral genome. Mod Pathol 1998; 11: 1252–6.

35. Perez-Montiel D, Hes O, Michal M et al. Micropapillary urothelial carcinoma of the upper urinary tract: clinicopathologic study of five cases. Am J Clin Pathol 2006; 126(1): 86–92.

36. Thiel DD, Igel TC, Wu KJ. Sarcomatoid carcinoma of transitional cell origin confined to renal pelvis. Urology 2006; 67(3): 622.

37. Holmang S, Thomsen J, Johansson SL. Micropapillary carcinoma of the renal pelvis and ureter. J Urol 2006; 175(2): 463–6.

38. Baydar D, Amin MB, Epstein JI. Osteoclast-rich undifferentiated carcinomas of the urinary tract. Mod Pathol 2006; 19(2): 161–71.

39. Hes O, Curik R, Mainer K et al. Urothelial signet-ring cell carcinoma of the renal pelvis with collagenous spherulosis: a case report. Int J Surg Pathol 2005; 13(4): 375–8.

40. Shimasaki N, Inoue K, Nishigawa H et al. Combined small cell carcinoma and sarcomatoid squamous cell carcinoma in the renal pelvis. Int J Urol 2005; 12(7): 686–9.

41. Acikalin MF, Kabukcuoglu S, Can C. Sarcomatoid carcinoma of the renal pelvis with giant cell tumor-like features: case report with immunohistochemical findings. Int J Urol 2005; 12(2): 199–203.

42. Shiga Y, Kawai K, Shimazui T et al. Case of alpha-fetoprotein-producing transitional cell carcinoma of the renal pelvis. Int J Urol 2004; 11(2): 117–18.

43. Onishi T, Franco OE, Shibahara T et al. Papillary adenocarcinoma of the renal pelvis and ureter producing carcinoembryonic antigen, carbohydrate antigen 19-9 and carbohydrate antigen 125. Int J Urol 2005; 12(2): 214–16.

44. Miyata Y, Kanda S, Nomata K et al. Expression of cyclooxygenase-2 and EP4 receptor in transitional cell carcinoma of the upper urinary tract. J Urol 2005; 173(1): 56–60.

45. Sauter G, Algaba F, Amin MB et al. Non-invasive urothelial neoplasias. In: Eble JN, Sauter G, Epstein JI, Sesterhenn I, eds. WHO Classification of Non-invasive Papillary Urothelial Tumors. In World Health Organization Classification of Tumors. Pathology and Genetics of Tumors of the Urinary System and Male Genital Organs. Lyon, France: IARCC Press; 2004.

46. Greene FL, Page DL, Fleming ID et al. AJCC Cancer Staging Manual. New York, Berlin, Heidelberg, Springer-Verlag; 2002.

47. Tsai YS, Tzai TS, Chow NH et al. Frequency and clinicopathologic correlates of ErbB1, ErbB2, and ErbB3 immunoreactivity in urothelial tumors of upper urinary tract. Urology 2005; 66(6): 1197–202.

48. Kamijima S, Tobe T, Suyama T et al. The prognostic value of p53, Ki-67 and matrix metalloproteinases MMP-2 and MMP-9 in transitional cell carcinoma of the renal pelvis and ureter. Int J Urol 2005; 12(11): 941–7.

49. Talwar N, Dargan P, Arora MP et al. Primary squamous cell carcinoma of the renal pelvis masquerading as pyonephrosis: a case report. Ind J Pathol Microbiol 2006; 49(3): 418–20.

50. Ng KF, Chuang CK, Chang PL et al. Absence of Epstein–Barr virus infection in squamous cell carcinoma of upper urinary tract and urinary bladder. Urology 2006; 68(4): 775–7.

51. Nogales FF, Andujar M, Lopez-Beltran A et al. Adenocarcinoma of the renal pelvis. Urol Int 1994; 52: 172–5.

52. Torres Gomez FJ, Torres Olivera FJ. Renal pelvis mucinous carcinoma. Case report. Arch Esp Urol 2006; 59(3): 300–2.

53. Nagahara A, Kawagoe M, Matsumoto F et al. Botryoid Wilms' tumor of the renal pelvis extending into the bladder. Urology 2006; 67(4): 845.

54. Ferrero Doria R, Garcia Victor F, Moreno Perez F et al. Cavernous haemangioma as the cause of ureteral pyelic junction obstruction. Arch Esp Urol 2005; 58(9): 960–3.

55. Kapusta L, Weiss MA, Lopez Beltran et al. Inflammatory myofibroblastic tumors of the kidney. Am J Surg Pathol 2003; 27: 658–66.

56. Ho PH, Chen SY, Hsueh C et al. Inflammatory myofibroblastic tumor of renal pelvis presenting with prolonged fever and abdominal pain in children: report of 1 case and review of literature. J Pediatr Surg 2005; 40(11): 35–7.

57. Hirsch MS, Dal Cin P, Fletcher CD. ALK expression in pseudosarcomatous myofibroblastic proliferations of the genitourinary tract. Histopathology 2006; 48(5): 569–78.

58. Peyromaure M, Mao K, Comperat E et al. Leiomyosarcoma of the renal pelvis. Prog Urol 2005; 15(3): 538–9.

59. Herawi M, Parwani AV, Edlow D et al. Glomus tumor of renal pelvis: a case report and review of the literature. Hum Pathol 2005; 36(3): 299–302.

60. Parada D, Moreira O, Gledhill T et al. Cellular pseudosarcomatous fibroepithelial stromal polyp of the renal pelvis. APMIS 2005; 113(1): 70–4.

61. Bozas G, Tassidou A, Moulopoulos LA et al. Non-Hodgkin's lymphoma of the renal pelvis. Clin Lymphoma Myeloma 2006; 6(5): 404–6.

62. Vizcaino JR, Macedo-Dias JA, Teixeira-de-Sousa JM et al. Pseudotumor of renal pelvis: Liesegang rings mimicking a solid neoplasm of the renal pelvis. Histopathology 2005; 47(1): 115–17.

63. Fine SW, Chan TY, Epstein JI. Inverted papillomas of the prostatic urethra. Am J Surg Pathol 2006; 30(8): 975–9.

64. Noel JC, Fayt I, Aguilar SF. Adenosquamous carcinoma arising in villous adenoma from female vulvar urethra. Acta Obstet Gynecol Scand 2006; 85(3): 373–6.

65. Kuroda N, Shiotsu T, Ohara M et al. Female urethral adenocarcinoma with a heterogeneous phenotype. APMIS 2006; 114(4): 314–18.

66. Achiche MA, Bouhaoula MH, Madani M et al. Primary transitional cell carcinoma of the bulbar urethra. Prog Urol 2005; 15(6): 1145–8.

67. Shalev M, Mistry S, Kernen K et al. Squamous cell carcinoma in a female urethral diverticulum. Urology 2002; 59(5): 773.

68. Hruby G, Choo R, Lehman M et al. Female clear cell adenocarcinoma arising within a urethral diverticulum. Can J Urol 2000; 7(6): 1160–3.

69. Velazquez EF, Soskin A, Bock A et al. Epithelial abnormalities and precancerous lesions of anterior urethra in patients with penile carcinoma: a report of 89 cases. Mod Pathol 2005; 18(7): 917–23.

70. Yvgenia R, Ben Meir D, Sibi J et al. Mucinous adenocarcinoma of posterior urethra. Report of a case. Pathol Res Pract 2005; 201(2): 137–40.

71. Cimentepe E, Bayrak O, Unsal A et al. Urethral adenocarcinoma mimicking urethral caruncle. Int Urogynecol J Pelvic Floor Dysfunct 2006; 17(1): 96–8.

72. Jayamohan Y, Urs L, Rowland RG et al. Periurethral carcinosarcoma: a report of 2 cases with a review of the literature. Arch Pathol Lab Med 2005; 129(4): 91–3.

73. Stein JP, Clark P, Miranda G et al. Urethral tumor recurrence following cystectomy and urinary diversion: clinical and pathological characteristics in 768 male patients. J Urol 2005; 173(4): 1163–8.

74. Wiedemann A, Muller H, Jaussi J et al. Mesonephric carcinoma of the urethra. A case report. Urologe A 2005; 44(4): 396–400.

75. Kato H, Kobayashi S, Islam AM et al. Female para-urethral adenocarcinoma: histological and immunohistochemical study. Int J Urol 2005; 12(1): 117–19.

76. Dell'Atti C, Missere M, Restaino G et al. Primary lymphoma of the female urethra. Rays 2005; 30(3): 269–72.

77. Chuang SS, Chiu AW, Liu H et al. Primary urethral MALT lymphoma with high proliferation fraction. Histopathology 2005; 46(6): 714–15.

78. Ozel B, Ballard C. Urethral and paraurethral leiomyomas in the female patient. Int Urogynecol J Pelvic Floor Dysfunct 2006; 17(1): 93–5.

79. Daneshmand S. Adenomatous polyp of the verumontanum causing bladder outlet obstruction. Sci World J 2004; 4(Suppl 1): 89–91.

80. Sanchez-Ortiz R, Huang SF, Tamboli P et al. Melanoma of the penis, scrotum and male urethra: a 40-year single institution experience. J Urol 2005; 173(6): 1958–65.

81. Simon R, Jones PA, Sidransky D et al. Genetics and predictive factors of non-invasive urothelial neoplasias. In: Eble JN, Sauter G, Epstein JI, Sesterhenn I, eds. WHO Classification of Non-invasive Papillary Urothelial Tumors. In World Health Organization Classification of Tumors. Pathology and Genetics of Tumors of the Urinary System and Male Genital Organs. Lyon, France: IARCC Press; 2004.

82. Hartmann A, Zanardo L, Bocker-Edmonston T et al. Frequent microsatellite instability in sporadic tumors of the upper urinary tract. Cancer Res 2002; 62(23): 6796–802.

83. Ericson KM, Isinger AP, Isfoss BL et al. Low frequency of defective mismatch repair in a population-based series of upper urothelial carcinoma. BMC Cancer 2005; 5: 23.

84. Maloney KE, Wiener JS, Walther PJ. Oncogenic human papillomaviruses are rarely associated with squamous cell carcinoma of the bladder: evaluation by differential polymerase chain reaction. J Urol 1994; 151(2): 360–4.

85. Wiener JS, Walther PJ. A high association of oncogenic human papillomaviruses with carcinomas of the female urethra: polymerase chain reaction-based analysis of multiple histological types. J Urol 1994; 151(1): 49–53.

86. Lopez-Beltran A, Escudero AL. Human papillomavirus and bladder cancer. Biomed Pharmacother 1997; 51(6–7): 252–7.

Index

Page numbers in *italic* denote figures or tables

Clinical Pathology of
UROLOGIC TUMORS

Edited by GREGOR MIKUZ

With increasing emphasis on the early diagnosis and management of urologic tumors, it is imperative that the practising urologist comprehend the relevance of the morphology for the clinical diagnostic and therapy. Moreover, the clinician should be fully informed of the importance of modern morphological methods (PCR, FISH, CGH etc) for the diagnosis and management of urological tumors.

Outstandingly illustrated, with over 300 colour pathological slides and clinical photos, *Clinical Pathology of Urologic Tumors* is presented as a highly attractive, coherently structured, full colour atlas, featuring sections on:

- **Renal tumors**
- **Adrenal glands**
- **Pathology of tumors of the urinary bladder**
- **Prostate cancer origins, diagnosis, and prognosis in clinical practice**
- **Tumors of the seminal vesicles**
- **Tumors of the testis and paratesticular structures**
- **Squamous cell carcinoma of the penis**
- **Handling of surgical specimens**
- **Pathology of tumors of the renal pelvis and ureter, and the urethra**
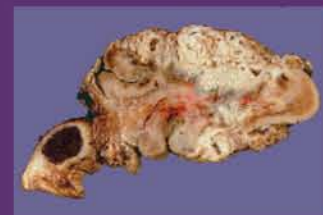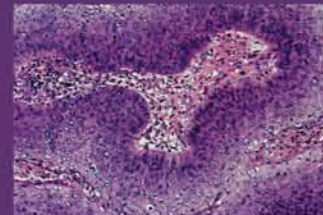
Clinical Pathology of Urologic Tumors is not only a necessary tool for the attending urologist, it will also satisfy the needs of oncologists, especially urololgic oncologists, residents in pathology or even pathologists, who are not daily faced with urological tumors.

Edited by Gregor Mikuz MD FRCPath, Professor of Pathology, Director, Institute of Pathology, Medical University Innsbruck, Innsbruck, Austria