CHAPTER 1

Tumours of the Kidney

Cancer of the kidney amounts to 2% of the total human cancer burden, with approximately 190,000 new cases diagnosed each year. They occur in all world regions, with a preference for developed countries. Etiological factors include environmental carcinogens (tobacco smoking) and lifestyle factors, in particular obesity.

Although renal tumours can be completely removed surgically, haematogeneous metastasis is frequent and may occur already at an early stage of the disease.

The pattern of somatic mutations in kidney tumours has been extensively investigated and has become, in addition to histopathology, a major criterion for classification. Kidney tumours also occur in the setting of several inherited cancer syndromes, including von Hippel-Lindau disease.
**WHO histological classification of tumours of the kidney**

<table>
<thead>
<tr>
<th>Renal cell tumours</th>
<th>Morphology code</th>
<th>WHO histological classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell renal cell carcinoma</td>
<td>8310/3</td>
<td>Haemangiopericytoma 9150/1</td>
</tr>
<tr>
<td>Multilocular clear cell renal cell carcinoma</td>
<td>8310/3</td>
<td>Osteosarcoma 9180/3</td>
</tr>
<tr>
<td>Papillary renal cell carcinoma</td>
<td>8260/3</td>
<td>Angiomyolipoma 8860/0</td>
</tr>
<tr>
<td>Chromophobe renal cell carcinoma</td>
<td>8317/3</td>
<td>Epithelioid angiomylipoma 8860/0</td>
</tr>
<tr>
<td>Carcinoma of the collecting ducts of Bellini</td>
<td>8319/3</td>
<td>Leiomyoma 8890/0</td>
</tr>
<tr>
<td>Renal medullary carcinoma</td>
<td>8319/3</td>
<td>Haemangiomia 9120/0</td>
</tr>
<tr>
<td>Xp11 translocation carcinomas</td>
<td>8319/3</td>
<td>Lymphangiomia 9170/0</td>
</tr>
<tr>
<td>Carcinoma associated with neuroblastoma</td>
<td>8319/3</td>
<td>Schwannoma 9560/0</td>
</tr>
<tr>
<td>Mucinous tubular and spindle cell carcinoma</td>
<td>8319/3</td>
<td>Solitary fibrous tumour 8815/0</td>
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<tr>
<td>Renal cell carcinoma, unclassified</td>
<td>8312/3</td>
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</tr>
<tr>
<td>Papillary adenoma</td>
<td>8260/0</td>
<td></td>
</tr>
<tr>
<td>Oncocytoma</td>
<td>8290/0</td>
<td></td>
</tr>
<tr>
<td>Metanephric tumours</td>
<td>8290/0</td>
<td></td>
</tr>
<tr>
<td>Metanephric adenoma</td>
<td>8325/0</td>
<td></td>
</tr>
<tr>
<td>Metanephric adenofibroma</td>
<td>9013/0</td>
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<tr>
<td>Metanephric stromal tumour</td>
<td>8935/1</td>
<td></td>
</tr>
<tr>
<td>Nephroblastic tumours</td>
<td>8960/3</td>
<td></td>
</tr>
<tr>
<td>Nephrogenic rests</td>
<td>8960/3</td>
<td></td>
</tr>
<tr>
<td>Nephroblastoma</td>
<td>8960/3</td>
<td></td>
</tr>
<tr>
<td>Cystic partially differentiated nephroblastoma</td>
<td>8959/1</td>
<td></td>
</tr>
<tr>
<td>Mesenchymal tumours</td>
<td>9044/3</td>
<td></td>
</tr>
<tr>
<td>Occurring Mainly in Children</td>
<td>8996/3</td>
<td></td>
</tr>
<tr>
<td>Clear cell sarcoma</td>
<td>9044/3</td>
<td></td>
</tr>
<tr>
<td>Rhabdoid tumour</td>
<td>8963/3</td>
<td></td>
</tr>
<tr>
<td>Congenital mesoblastic nephroma</td>
<td>8960/1</td>
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<td>Ossifying renal tumour of infants</td>
<td>8967/0</td>
<td></td>
</tr>
<tr>
<td>Occurring Mainly in Adults</td>
<td>8898/3</td>
<td></td>
</tr>
<tr>
<td>Leiomyosarcoma (including renal vein)</td>
<td>8898/3</td>
<td></td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>9120/3</td>
<td></td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>8900/3</td>
<td></td>
</tr>
<tr>
<td>Malignant fibrous histiocytoma</td>
<td>8830/3</td>
<td></td>
</tr>
</tbody>
</table>

1 Morphology code of the International Classification of Diseases for Oncology (ICD-O) (840) and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.
## TNM classification of renal cell carcinoma

<table>
<thead>
<tr>
<th><strong>TNM classification</strong></th>
<th><strong>N</strong> – Regional Lymph Nodes</th>
<th><strong>M</strong> – Distant Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T</strong> – Primary Tumour</td>
<td><strong>NX</strong> Regional lymph nodes cannot be assessed</td>
<td><strong>MX</strong> Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>TX</td>
<td><strong>N0</strong> No regional lymph node metastasis</td>
<td><strong>M0</strong> No distant metastasis</td>
</tr>
<tr>
<td>T0</td>
<td><strong>N1</strong> Metastasis in a single regional lymph node</td>
<td><strong>M1</strong> Distant metastasis</td>
</tr>
<tr>
<td>T1</td>
<td><strong>N2</strong> Metastasis in more than one regional lymph node</td>
<td></td>
</tr>
<tr>
<td>T1a</td>
<td>Tumour 7 cm or less in greatest dimension, limited to the kidney</td>
<td></td>
</tr>
<tr>
<td>T1b</td>
<td>Tumour 4 cm or less</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Tumour more than 4 cm but not more than 7 cm</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Tumour more than 7 cm in greatest dimension, limited to the kidney</td>
<td></td>
</tr>
<tr>
<td>T3a</td>
<td>Tumour extends into major veins or directly invades adrenal gland or perinephric tissues but not beyond Gerota fascia</td>
<td></td>
</tr>
<tr>
<td>T3b</td>
<td>Tumour directly invades adrenal gland or perinephric tissues* but not beyond Gerota fascia</td>
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<tr>
<td>T3c</td>
<td>Tumour grossly extends into renal vein(s)* or vena cava or its wall below diaphragm</td>
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</tr>
<tr>
<td>T4</td>
<td>Tumour grossly extends into vena cava or its wall above diaphragm</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>Tumour directly invades beyond Gerota fascia</td>
<td></td>
</tr>
<tr>
<td><strong>Notes:</strong> 1 Includes renal sinus (peripelvic) fat</td>
<td>2 Includes segmental (muscle-containing) branches</td>
<td></td>
</tr>
</tbody>
</table>

### Stage grouping

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
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<td>M0</td>
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<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>T1, T2, T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Any T</td>
<td>N0, N1</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>Any T</td>
<td>N2</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td></td>
</tr>
</tbody>
</table>

1 (044,2662).
2 A help desk for specific questions about the TNM classification is available at http://www.uicc.org/tnm
Renal cell carcinoma

Definition
Renal cell carcinoma is a group of malignancies arising from the epithelium of the renal tubules.

Epidemiology of renal cell cancer
Renal cell cancer (RCC) represents on average over 90% of all malignancies of the kidney that occur in adults in both sexes. Overall it is the 12th most common site in men and 17th in women. In males living in industrialized areas including Japan, it is as common as non-Hodgkin lymphoma ranking 6th, while in less developed areas it ranks 16th, in the same order of magnitude as carcinoma of the nasopharynx. In women it ranks 12th and 17th in developed and developing countries respectively [749]. The incidence is low in the African and Asian continents but not in Latin America where around 1995 Uruguay recorded one of the highest rates in the world. The highest rates in both men and women were observed in the Czech Republic with 20 and 10 annual new cases per 100,000 population respectively, age standardized [2016]. The lowest rates recorded were less that 1 new case per 100,000 showing a 10-fold variation in the risk of the disease. The latest systematic analyses of time trends of the incidence of kidney cancer indicate a general increase in both sexes in all monitored regions, up until the mid-80s [481]. These trends were paralleled by mortality, which thereafter began to slow down or even fall in some high risk countries [2843]. After the low peak in children due to nephroblastoma, the incidence of renal cell cancer increases steadily after age 40 years as most epithelial tumours but the risk levels off or even declines from age 75 in both sexes. It is two to three times more common in men than in women in both high and low risk countries [2016].

Etiology
Tobacco smoking is a major cause of kidney cancer and accounts for at least 39% of all cases in males [2015]. Exposure to carcinogenic arsenic compounds in industrial processes or through drinking water increases the risk of renal cancer by 30% [1150]. Several other environmental chemicals have been addressed as possible carcinogens for the kidney but definitive evidence has not been established. These include asbestos, cadmium, some organic solvents, pesticides and fungal toxins. Some steroidal estrogens and the nonsteroidal diethylstilboestrol induce tumours in hamster [1150,1154], but to date an excess has not been reported in exposed humans. Estrogens could be involved in the mechanism that induces RCC in overweight and obese individuals. Several epidemiological studies both prospective and retrospective, conducted in many different populations have established that the risk of kidney cancer increases steadily with increasing body mass index (BMI), the most common measure of overweight [1156]. The incidence of RCC in obese people (BMI>29 kg/m²) is double that of normal individuals and about 50% increased if overweight (BMI 25-30 kg/m²) [221]. The same authors estimated that in Europe...
one quarter of kidney cancers in both sexes are attributable to excess weight. The association has been reported as stronger in women than in men in some but not all studies.

The incidence of RCC is significantly increased in people with a history of blood hypertension that is independent of obesity and tobacco smoking (458,962,2912). The association with the use of diuretics instead is referable to hypertension, while a small but consistent excess of RCC has been established with exposure to phenacetin-containing analgesics that also cause cancer of the renal pelvis (1150).

Parity is a factor that has been investigated in several studies but results are discordant (1430). A real association would be supported by estrogen-mediated carcinogenesis that is documented in animal models. Conversely, it could be a confounded effect of excess body weight that is often increased in women who had many children. Other exposures that have been addressed are a family history of kidney cancer (829), birth weight (221), low consumption of fruits and vegetables (2841) and the use of antihypertensive drugs other than diuretics. The significance of these associations remain however unclear.

Few studies have investigated the hypothesis that genetic characteristics may modulate the effect of exposure to chemical carcinogens. In one study the effect of tobacco smoking was stronger in subjects with slow acetylator genotypes as defined by polymorphisms in the N-acetyltransferase 2 gene that is involved in the metabolism of polycyclic aromatic hydrocarbons (2359). Conversely, RCC was not associated with the glutathione S-transferase (GST)

Clinical features
Signs and symptoms
Haematuria, pain, and flank mass are the classic triad of presenting symptoms, but nearly 40% of patients lack all of these and present with systemic symptoms, including weight loss, abdominal pain, anorexia, and fever (870). Elevation of the erythrocyte sedimentation rate occurs in approximately 50% of cases (634). Normocytic anaemia unrelated to haematuria occurs in about 33% (438,902). Hepatosplenomegaly, coagulopathy, elevation of serum alkaline phosphatase, transaminase, and alpha-2-globulin concentrations may occur in the absence of liver metastases and may resolve when the renal tumour is resected (1441). Systemic amyloidosis of the AA type occurs in about 3% of patients (2705).

Renal cell carcinoma may induce paraneoplastic endocrine syndromes (1441,2525), including humoral hypercalcaemia of malignancy (pseudohyperparathyroidism), erythrocytosis, hypertension, and gynecomastia. Hypercalcaemia without bone metastases occurs in approximately 10% of patients and in nearly 20% of patients with disseminated carcinoma (736). In about 66% of patients, erythropoietin concentration is elevated (2526), but less than 4% have erythrocytosis (902,2526). Approximately 33% are hypertensive, often with elevated renin concentrations in the renal vein of the tumour-bearing
Kidney (902,2491). Gynecomastia may result from gonadotropin (904) or prolactin production (2486). Renal cell carcinoma also is known for presenting as metastatic carcinoma of unknown primary, sometimes in unusual sites.

**Imaging**

The current imaging technology has altered the management of renal masses as it enables detection and characterization of very small masses. Radiological criteria established by Bosniak assist management of renal masses (283). Ultrasonography is useful for detecting renal lesions and if it is not diagnostic of a simple cyst, CT before and after IV contrast is required. Plain CT may confirm a benign diagnosis by identifying fat in angiomyolipoma (284). Lesions without enhancement require nothing further, but those with enhancement require follow-ups at 6 months, 1 year, and then yearly (258). Increased use of nephron-sparing and laparoscopic surgery underscores the importance of preoperative imaging work-up. Routine staging work-up for renal cell carcinoma includes dynamic CT and chest radiography.
Familial renal cell carcinoma

The kidney is affected in a variety of inherited cancer syndromes. For most of them, the oncogene / tumour suppressor gene involved and the respective germline mutations have been identified, making it possible to confirm the clinical diagnosis syndrome, and to identify asymptomatic gene carriers by germline mutation testing (2510). Each of the inherited syndromes predisposes to distinct types of renal carcinoma. Usually, affected patients develop bilateral, multiple renal tumours; regular screening of mutation carriers for renal and extrarenal manifestations is considered mandatory.

Von Hippel-Lindau disease (VHL)

**Definition**
The von Hippel-Lindau (VHL) disease is inherited through an autosomal dominant trait and characterized by the development of capillary haemangioblastomas of the central nervous system and retina, clear cell renal carcinoma, phaeochromocytoma, pancreatic and inner ear tumours. The syndrome is caused by germline mutations of the VHL tumour suppressor gene, located on chromosome 3p25-26. The VHL protein is involved in cell cycle regulation and angiogenesis.

Approximately 25% of haemangioblastomas are associated with VHL disease (1883).

**MIM No.** 193300 (1679).

**Synonyms and historical annotation**
Lindau (1506) described capillary haemangioblastoma, and also noted its association with retinal vascular tumours, previously described by von Hippel (2752), and tumours of the visceral organs, including kidney.

**Incidence**
Von Hippel-Lindau disease is estimated

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### Table 1.01
Major inherited tumour syndromes involving the kidney. Modified, from C.P. Pavlovich et al. (2003)

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene Protein</th>
<th>Chromosome</th>
<th>Kidney</th>
<th>Skin</th>
<th>Other tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td>von Hippel-Lindau</td>
<td>VHL</td>
<td>3p25</td>
<td>Multiple, bilateral clear-cell renal cell carcinoma (CCRCC), renal cysts</td>
<td>-</td>
<td>Retinal and CNS haemangioblastomas, phaeochromocytoma, pancreatic cysts and neuroendocrine tumours, endolymphatic sac tumours of the inner ear, epididymal and broad ligament cystadenomas</td>
</tr>
<tr>
<td>Hereditary papillary renal cancer</td>
<td>c-MET</td>
<td>7q31</td>
<td>Multiple, bilateral papillary renal cell carcinomas (PRCC) Type 1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hereditary leiomyomatosis and RCC</td>
<td>FH</td>
<td>1q42-43</td>
<td>Papillary renal cell carcinoma (PRCC), non-Type 1</td>
<td>Nodules (leiomyomas)</td>
<td>Uterine leiomyomas and leiomyosarcomas</td>
</tr>
<tr>
<td>Birt-Hogg-Dubé</td>
<td>BHD Folliculin</td>
<td>17p11.2</td>
<td>Multiple chromophobe RCC, conventional RCC, hybrid oncocytoma, papillary RCC, oncocytic tumours</td>
<td>Facial fibrofolliculomas</td>
<td>Lung cysts, spontaneous pneumothorax</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>TSC1</td>
<td>9q34</td>
<td>Multiple, bilateral angiomylolipomas, lymphangioleiomyomatosis</td>
<td>Cutaneous angiolfibroma (’adenoma sebaceum’) peau chagrin, subungual fibromas</td>
<td>Cardiac rhabdomyomas, adenomatous polyps of the duodenum and the small intestine, lung and kidney cysts, cortical tubers and subependymal giant cell astrocytomas (SEGA)</td>
</tr>
<tr>
<td>Constitutional chromosome 3 translocation</td>
<td>Unknown</td>
<td></td>
<td>Multiple, bilateral clear-cell renal cell carcinomas (CCRCC)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Familial renal cell carcinoma
Diagnostic criteria
The clinical diagnosis of von Hippel-Lindau disease is based on the presence of capillary haemangioblastoma in the CNS or retina, and the presence of one of the typical VHL-associated extraneural tumours or a pertinent family history. In VHL disease, germline VHL mutations can virtually always be identified (2510).

Kidney tumours associated with VHL
The typical renal manifestation of VHL are kidney cysts and clear-cell renal cell carcinomas (CCRCC). Multiple kidney tumours of other histological types rule out the diagnosis of VHL (2032). Histological examination of macroscopically inconspicuous renal tissue from VHL patients may reveal several hundred independent tumours and cysts (2773).

Clinical Features
Renal lesions in carriers of VHL germline mutations are either cysts or CCRCC. They are typically multifocal and bilateral. The mean age of manifestation is 37 years versus 61 years for sporadic CCRCC, with an onset age of 16 to 67 years (2032). There is a 70% chance of developing CCRCC by the age of 70 years (1597). The diagnostic tools of choice are CT and MR imaging. Metastatic RCC is the leading cause of death from VHL (2384).

The median life expectancy of VHL patients was 49 years (1279,1883). In order to detect VHL-associated tumours in time, analyses for germline mutations of the VHL gene have been recommended in every patient with retinal or CNS haemangioblastoma, particularly in those of younger age and with multiple lesions. Periodic screening of VHL patients by MRI should start after the age of ten years (328).

Extrarenal manifestations
Retinal haemangioblastomas manifest earlier than kidney cancer (mean age, 25 years) and thus offer the possibility of an early diagnosis. CNS haemangioblastomas develop somewhat later (mean, 30 years); they are predominantly located in the cerebellum, further in brain stem and spinal chord. Both lesions are benign and rarely life threatening. Phaeochromocytomas may constitute a major clinical challenge, particularly in VHL families with predisposition to the development of these tumours. They are often associated with pancreatic cysts. Other extrarenal manifestations include neuroendocrine tumours, endolymphatic sac tumours of the inner ear, and epididymal and broad ligament cystadenomas.

Genetics
The VHL gene is located at chromosome 3p25–26. The VHL tumour suppressor gene has three exons and a coding sequence of 639 nucleotides (1445).

Gene expression
The VHL gene is expressed in a variety of human tissues, in particular epithelial cells of the skin, the gastrointestinal, respiratory and urogenital tract and endocrine and exocrine organs (500,2277). In the CNS, immunoreactivity for pVHL is prominent in neurons, including Purkinje cells of the cerebellum (1559,1864).

Function of the VHL protein
Mutational inactivation of the VHL gene in affected family members is responsible for the development of von Hippel-Lindau disease. The VHL tumour suppressor gene has three exons and a coding sequence of 639 nucleotides (1445).
Induction of EPO is responsible for the tumorizing anti-VEGF antibody [1654]. VEGF has been targeted as a component of VHL associated neoplasms which the suppressor gene product, the VHL protein (pVHL), causes neoplastic transformation, have remained enigmatic. Several signalling pathways appear to be involved [1942], one of which points to a role of pVHL in protein degradation and angiogenesis. The alpha domain of pVHL forms a complex with elongin B, elongin C, Cul-2 [1533,2028,2488] and Rbx1 [1264] which has ubiquitin ligase activity [1188], thereby targeting cellular proteins for ubiquitination and proteasome-mediated degradation. The domain of the VHL gene involved in the binding to elongin is frequently mutated in VHL-associated neoplasms [2488]. The beta-domain of pVHL interacts with the alpha subunits of hypoxia-inducible factor 1 (HIF-1) which mediates cellular responses to hypoxia. Under normoxic conditions, the beta subunit of HIF is hydroxylated on to one of two proline residues. Binding of the hydroxylated subunit pVHL causes polyubiquitination and thereby targets HIF-alpha for proteasome degradation [855]. Under hypoxic conditions or in the absence of functional VHL, HIF-alpha accumulates and activates the transcription of hypoxia-inducible genes, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF-beta), transforming growth factor (TGF-alpha) and erythropoietin (EPO). Constitutive overexpression of VEGF explains the extraordinary capillary component of VHL associated neoplasms [1650]. VEGF has been targeted as a novel therapeutic approach using neutralizing anti-VEGF antibody [1654]. Induction of EPO is responsible for the occasional paraneoplastic erythrocytosis in patients with kidney cancer and CNS haemangioblastoma.

Table 1.02
Genotype - phenotype correlations in VHL patients.

<table>
<thead>
<tr>
<th>VHL-type</th>
<th>Phenotype</th>
<th>Predisposing mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Without phaeochromocytoma</td>
<td>686 T -&gt; C Leu -&gt; Pro</td>
</tr>
<tr>
<td>Type 2A</td>
<td>With phaeochromocytoma and renal carcinoma</td>
<td>712 C -&gt; T Arg -&gt; Trp</td>
</tr>
<tr>
<td>Type 2B</td>
<td>With phaeochromocytoma but without renal cell carcinoma</td>
<td>505 T -&gt; C Tyr -&gt; His, 658 G -&gt; T Ala -&gt; Ser</td>
</tr>
</tbody>
</table>

for their genetic susceptibility to renal cell carcinoma and capillary haemangioblastoma, but the mechanisms by which the suppressor gene product, the VHL protein (pVHL), causes neoplastic transformation, have remained enigmatic. Several signalling pathways appear to be involved [1942], one of which points to a role of pVHL in protein degradation and angiogenesis. The alpha domain of pVHL forms a complex with elongin B, elongin C, Cul-2 [1533,2028,2488] and Rbx1 [1264] which has ubiquitin ligase activity [1188], thereby targeting cellular proteins for ubiquitination and proteasome-mediated degradation. The domain of the VHL gene involved in the binding to elongin is frequently mutated in VHL-associated neoplasms [2488]. The beta-domain of pVHL interacts with the alpha subunits of hypoxia-inducible factor 1 (HIF-1) which mediates cellular responses to hypoxia. Under normoxic conditions, the beta subunit of HIF is hydroxylated on to one of two proline residues. Binding of the hydroxylated subunit pVHL causes polyubiquitination and thereby targets HIF-alpha for proteasome degradation [855]. Under hypoxic conditions or in the absence of functional VHL, HIF-alpha accumulates and activates the transcription of hypoxia-inducible genes, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF-beta), transforming growth factor (TGF-alpha) and erythropoietin (EPO). Constitutive overexpression of VEGF explains the extraordinary capillary component of VHL associated neoplasms [1650]. VEGF has been targeted as a novel therapeutic approach using neutralizing anti-VEGF antibody [1654]. Induction of EPO is responsible for the occasional paraneoplastic erythrocytosis in patients with kidney cancer and CNS haemangioblastoma.

Additional functions of the VHL protein may contribute to malignant transformation and the evolution of the phenotype of VHL associated lesions. Recent studies in renal cell carcinoma cell lines suggest that pVHL is involved in the control of cell cycle exit, i.e. the transition from the G2 into quiescent G0 phase, possibly by preventing accumulation of the cyclin-dependent kinase inhibitor p27 [2027]. Another study showed that only wild-type but not tumour-derived pVHL binds to fibronectin. As a consequence, VHL-/ renal cell carcinoma cells showed a defective assembly of an extracellular fibronectin matrix [1943]. Through a down-regulation of the response of cells to hepatocyte growth factor / scatter factor and reduced levels of tissue inhibitor of metalloproteinase 2 (TIMP-2), pVHL deficient tumours cells exhibit a significantly higher capacity for invasion [1353]. Further, inactivated pVHL causes an overexpression of transmembrane carbonic anhydrases that are involved in extracellular pH regulation [1186] but the biological significance of this dysregulation remains to be assessed.

Gene mutations and VHL subtypes
Germline mutations of the VHL gene are spread all over the three exons. Missense mutations are most common, but nonsense mutations, microdeletions / insertions, splice site mutations and large deletions also occur [1882, 1958, 2927]. The spectrum of clinical manifestations of VHL reflects the type of germline mutation. Phenotypes are based on the absence (type 1) or presence (type 2) of phaeochromocytoma.

VHL type 2 is usually associated with missense mutations and subdivided on the presence (type 2A) or absence (2B) of renal cell carcinoma [136,421, 893,1883]. In contrast to loss of function variants in VHL type 1, mutations predisposing to phaeochromocytoma (VHL type 2) are mainly of the missense type predicted to give rise to conformationally changed pVHL [2804,2927]. In addition, VHL type 2C has been used for patients with only phaeochromocytoma [2201, 2804]; however several years later some of these cases developed other VHL manifestations. According to its function as a tumour suppressor gene, VHL gene mutations are also common in sporadic haemangioblastomas and renal cell carcinomas [1268,1931].

Hereditary papillary renal carcinoma (HPRC)

Definition
Hereditary papillary renal carcinoma (HPRC) is an inherited tumour syndrome characterized with an autosomal dominant trait, characterized by late onset, multiple, bilateral papillary renal cell tumours.

MIM No. 179755 [1679].

Diagnostic criteria
The diagnosis of HPRC is based on the occurrence of multiple, bilateral kidney tumours. It has been estimated that approximately 50% of affected family...
members develop the disease by the age of 55 years. Extrarenal manifestations of HPRC have not been identified.

Papillary renal cell carcinoma
BHD patients develop myriad papillary tumours, ranging from microscopic lesions to clinically symptomatic carcinomas (1979). The histological pattern has been termed papillary renal carcinoma type 1 and is characterized by papillary or tubulo-papillary architecture very similar to papillary renal cell carcinoma, type 1.

Genetics
Responsible for the disease are activating mutations of the MET oncogene which maps to chromosome 7q31. MET codes for a receptor tyrosine kinase (799,1212,1213,1570,2326,2327,2926,2928). Its ligand is hepatocyte growth factor (HGFR). Mutations in exons 16 to 19, ie the tyrosine kinase domain cause a ligand-independent constitutive activation.

Duplication of the mutant chromosome 7 leading to trisomy is present in a majority of HPRC tumours (768,845,1996,2032,2937).

Management
For patients with confirmed germline mutation, annual abdominal CT imaging is recommended.

Hereditary leiomyomatosis and renal cell cancer (HLRCC)

Definition
Hereditary leiomyomatosis and renal cell cancer (HLRCC, MIN no: 605839) is an autosomal dominant tumour syndrome caused by germline mutations in the FH gene. It is characterized by predisposition to benign leiomyomas of the skin and the uterus. Predisposition to renal cell carcinoma and uterine leiomyosarcoma is present in a subset of families.

MIM No. 605839 [1679].

Diagnostic criteria
The definitive diagnosis of HLRCC relies on FH mutation detection. The presence of multiple leiomyomas of the skin and the uterus papillary type 2 renal cancer, and early-onset uterine leiomyosarcoma are suggestive (51,52,1330,1450,1469,2632).

Renal cell cancer
At present, 26 patients with renal carcinomas have been identified in 11 families out of 105 (10%) (52,1329,1450,1469,2632). The average age at onset is much earlier than in sporadic kidney cancer; median 36 years in the Finnish and 44 years in the North American patients, (range 18-90 years). The carcinomas are typically solitary and unilateral (1450,2632). The most patients have died of metastatic disease within five years after diagnosis. The peculiar histology of renal cancers in HLRCC originally led to identification of this syndrome (1450).

Typically, HLRCC renal cell carcinomas display papillary type 2 histology and large cells with abundant eosinophilic cytoplasm, large nuclei, and prominent inclusion-like eosinophilic nucleoli. The Fuhrman nuclear grade is from 3 to 4. Most tumours stain positive for vimentin and negative for cytokeratin 7. Recently, three patients were identified having either collective duct carcinoma or oncocytic tumour (52,2632). Regular screening for kidney cancer is recommended, but optimal protocols have not yet been determined. Computer tomography and abdominal ultrasound have been proposed (1328,2632). Moreover, as renal cell carcinoma is present only in a subset of families, there are no guidelines yet, whether the surveillance should be carried out in all FH mutation families.

Leiomyomas of the skin and uterus
Leiomyomas of the skin and uterus are the most common features of HLRCC, the penetrance being approximately 85% (1328,2632). The onset of cutaneous leiomyomas ranges from 10-47 years, and uterine leiomyomas from 18-52 years (mean 30 years) (2632). Clinically, cutaneous leiomyomas present
as multiple firm, skin-coloured nodules ranging in size from 0.5-2 cm. Uterine leiomyomas in HLRCC are often numerous and large. Cutaneous leiomyomas are composed of interlacing bundles of smooth muscle cells with centrally located blunt-ended nucleus. Uterine leiomyomas are well-circumscribed lesions with firm and fibrous appearance. Histologically, they are composed of interlacing bundles of elongated, eosinophilic smooth muscle cells surrounded by well-vascularized connective tissue. Leiomyomas with atypia may also occur.

**Leiomyosarcoma of the uterus**

Predisposition to uterine leiomyosarcoma is detected in a subset of HLRCC families (3 out of 105 families) {1450,1469}. The cases have been diagnosed at 30-39 years. Uterine leiomyosarcomas invade the adjacent myometrium and are not well demarcated from normal tissue. The tumours are densely cellular and display spindle cells with blunt-ended nuclei, eosinophilic cytoplasm, and a variable degree of differentiation.

**Genetics**

*Gene structure and function*

FH is located in chromosome 1q42.3-q43, consists of 10 exons, and encodes a 511 amino acid peptide. The first exon encodes a mitochondrial signal peptide. {661,662,2623}, but processed FH (without the signal peptide) is present also in the cytosol. Mitochondrial FH acts in the tricarboxylic acid (Krebs) cycle catalyzing conversion of fumarate to malate. FH is also known to be involved in the urea cycle. However, the role of cytosolic FH is still somewhat unclear. Biallelic inacti-

---

**Fig. 1.11** A Multiple cutaneous leiomyomas in a female HLRCC patient. B Fumarate hydratase (FH) gene mutations in HLRCC and FH deficiency. Mutated codons identified in the families with RCC and/or uterine leiomyosarcoma are indicated.

**Fig. 1.12** Hereditary leiomyoma renal cell carcinoma (HLRCC). A Renal cell carcinoma from a 50 year old female patient displaying papillary architecture resembling papillary renal cell carcinoma, type 2 (H&E staining, magnification x10). B Thick papillae are covered by tall cells with abundant cytoplasm, large pseud stratified nuclei and prominent nucleoli.
vation of FH has been detected in almost all HLRCC tumours [52, 1329, 1330, 1450].

FH mutations
Germline mutations in FH have been found in 85% (89/105) of the HLRCC families [52, 1330, 1469, 2627, 2632]. Altogether 50 different germline mutations have been identified. Two founder mutations have been detected in the Finnish population, a missense mutation H153R (in 3 out of 7 families) and a 2-bp deletion in codon 181 (in 3 out of 7 families). Most of the families with these mutations included renal cell cancer and/or uterine leiomyosarcoma [1330, 1469, 2627]. A splice site mutation IVS4+1G>A was detected in families of Iranian origin [465]. In addition, a missense mutation R190H was reported in 35% of the families from North America. To date, the role of FH in sporadic tumorigenesis has been evaluated in three different studies [169, 1330, 1469]. Somatic FH mutations seem to be rare, but have been found in uterine leiomyomas and a high-grade sarcoma.

FH deficiency
This is a recessive disease caused by biallelic germline mutations in FH. The syndrome is characterized by neurological impairment, growth and developmental delay, fumaric aciduria and absent or reduced enzyme activity in all tissues. Heterozygous parents are neurologically asymptomatic heterozygous carriers of the mutation with a reduced enzyme activity (approximately 50%). Tumour predisposition similar to HLRCC is likely [2627]. Thus far, 10 different FH mutations have been reported in 14 FH deficiency families (Fig 3.).

Genotype-phenotype correlations
No clear pattern has emerged to date. Three mutations (K187R, R190C, and R190H) have been reported in both HLRCC and FH deficiency. Renal cell cancer and uterine leiomyosarcoma occur only in a minority of families, but the same mutations (a 2-bp deletion in codon 181, R190H, and H275Y) have been identified in families with or without malignancies. Because some families appear to have high risk of cancer at early age, and others little or no risk, modifying gene/s could play a key role in the development of renal cancer and uterine leiomyosarcoma in HLRCC [697, 2627, 2632].

Birt-Hogg-Dubé syndrome (BHD)
The BHD syndrome conveys susceptibility to develop renal epithelial tumours resembling mainly chromophobe and clear cell renal carcinomas and renal oncocytes as well as fibrofolliculomas and pulmonary cysts [246, 1891, 2033, 2631, 2924].

Definition
Birt-Hogg-Dubé (BHD) syndrome is a syndrome characterised by benign skin tumours, specifically fibrofolliculomas, trichodiscomas and acrochordons. Multiple renal tumours and spontaneous pneumothoraces are frequent in patients with BHD syndrome.

MIM No. 135150 (1679).

Diagnostic criteria
Renal tumours
Renal pathology may vary in individuals with BHD syndrome. Tumours can be multiple and bilateral. Renal oncocyta is well described and is usually thought of as a benign tumour. Other histopathologies have been described including papillary and chromophobe adenocarcinoma with a mixed population of clear and eosinophilic cells. The age at clinical manifestation is approximately 50 years and the mean number of tumours present is 5 per patient. Metastatic disease is rare and appears to only occur if the primary tumour has a diameter of >3 cm [2031].

Skin tumours
Fibrofolliculomas (FF), trichodiscomas (TD) and acrochordons are the classical skin lesions in BHD syndrome. The FF and TD lesions look the same and present as smooth dome-shaped, skin coloured papules up to 5mm in diameter over the face, neck and upper body with onset typically in the third or fourth decade of life. Skin lesions are initially subtle but remain indefinitely and become more obvious with increasing age as illustrated by Toro et al 1999 [2631]. Acrochordons (skin tags) are not always present. Biopsy will usually demonstrate an epidermis with aberrant follicular structures, thin columns of epithelial cells and small immature sebocytes clustered within the epithelial cords. Alcian blue demonstrates the presence of abundant mucin within the stroma.

Other lesions
Spontaneous pneumothorax and the
presence of pulmonary cysts are recognised features of BHD syndrome. Multiple lipomas and mucosal papules have been described (2361). A reported association with colonic neoplasia has not been confirmed in subsequent studies, there may be a slight increase in the incidence of other neoplasia although this remains unclear (1307).

**Genetics**

BHD syndrome is a rare autosomal dominant condition with incomplete penetrance. The BHD gene maps to chromosome 17p11.2 (1306,2328). It codes for a novel protein called folliculin whose function is unknown currently (1891). Affected family members typically show frameshift mutations, ie insertions, stop codons, deletions (1891). A mutational hot spot present in more than 40% of families was identified in a tract of 8 cytosines (2032).

LOH analyses and assessment of promoter methylation indicate that BHD is also involved in the development of a broad spectrum of sporadic renal cancers (1308).

**Management**

Surveillance for all first-degree relatives of an affected individual is advocated. Skin examination to determine diagnosis from the third decade. For those with skin features or found to have the characteristic dermatological features, annual renal MRI scan would be the investigation of choice to detect any renal malignancy at as early a stage as possible and to facilitate minimal renal surgery where possible to conserve renal function. In tumour predisposition syndromes where a second somatic mutation in the normally functioning wild type gene will leave no functioning protein in the cell, repeated examinations involving ionising radiation may carry a risk of inducing malignancy.

**Constitutional chromosome 3 translocations**

**Definition**

Inherited cancer syndrome caused by constitutional chromosome 3 locations with different break points, characterized by an increased risk of developing renal cell carcinomas (RCC).

<table>
<thead>
<tr>
<th>Translocation</th>
<th>Number of RCC cases</th>
<th>Generations Involved</th>
<th>Mean age</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(3;8)(p14;q24)</td>
<td>10</td>
<td>4</td>
<td>44</td>
<td>Cohen et al. (476)</td>
</tr>
<tr>
<td>t(3;6)(p13;q25.1)</td>
<td>1</td>
<td>3</td>
<td>50</td>
<td>Kovacs et al (1371)</td>
</tr>
<tr>
<td>t(2;3)(q35;q21)</td>
<td>5</td>
<td>3</td>
<td>47</td>
<td>Koolen et al. (1355)</td>
</tr>
<tr>
<td>t(3;6)(q12;q15)</td>
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<td>4</td>
<td>57.5</td>
<td>Geurts van Kessel et al. (862)</td>
</tr>
<tr>
<td>t(3;4)(p13;p16)</td>
<td>1</td>
<td>3</td>
<td>52</td>
<td>Geurts van Kessel et al. (862)</td>
</tr>
<tr>
<td>t(2;3)(q33;q21)</td>
<td>7</td>
<td>3</td>
<td>n.i.</td>
<td>Zajaczek et al. (2917)</td>
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<tr>
<td>t(1;3)(q32;q13.3)</td>
<td>4</td>
<td>4</td>
<td>66.7</td>
<td>Kanayama et al. (1285)</td>
</tr>
</tbody>
</table>

MIM No. 144700 (1679).

**Diagnostic criteria**

Occurrence of single or multiple, unilateral or bilateral RCC in a member of a family with a constitutional chromosome 3 translocation. The association of RCC with a chromosome 3 translocation alone is not diagnostic since this genetic alteration is also observed in sporadic cases.

**Pathology**

Tumours show histologically the typical features of clear cell RCC.

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**Table 1.03**

Familial renal cell cancer associated with chromosome 3 constitutional translocation. From F. van Erp et al. (2695).

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**Fig. 1.14** Birt-Hogg-Dubé syndrome (BHD). A Hybrid oncocytic tumour composed of a mixture of clear cells and cells with abundant eosinophilic cytoplasm. B Small cluster of clear cells is surrounded by normal tubules. These lesions can be found scattered through the renal parenchyma.
Genetics

The first family was described by Cohen et al. (476) with 10 RCC patients over 4 generations. All patients were carriers of a t(3;8)(p14;q24). In a second RCC family a t(3;6)(p13;q25) was found to segregate and, as yet, only one person in the first generation developed multiple bilateral RCCs (1371). Additionally, a single sporadic case with a constitutional t(3;12)(q13;q24) was reported (1374). Seven families have now been reported; translocations are different but in all families the breakpoints map to the proximal p- and q-arms of chromosome 3. Affected family members carry a balanced chromosomal translocation involving chromosome 3. The mode of inheritance is autosomal dominant. Translocations vary among different families and this may affect penetrance. Loss of the derivative chromosome 3 through genetic instability is considered the first step in tumour development, resulting in a single copy of VHL. The remaining VHL copy may then be mutated or otherwise inactivated. However, this mechanism involving VHL is hypothetical as affected family members do not develop extra-renal neoplasms or other VHL manifestations. The identification of at least 7 families strongly supports the notion that constitutional chromosome 3 translocations may substantially increase the risk to develop renal cell carcinoma and this should be taken into account in the framework of genetic counselling.

Fig. 1.15 Diagram of chromosome 3 with seven constitutional chromosome 3 translocations and the respective breakpoint positions (left). On the right side, breakpoint frequencies (%) of chromosome 3 translocations in 93 Dutch families are shown (grey bars), in addition to somatic chromosome 3 translocations in 157 sporadic RCCs (black bars). From F. van Erp et al. (2695).
Clear cell renal cell carcinoma

Definition
Clear cell renal cell carcinoma is a malignant neoplasm composed of cells with clear or eosinophilic cytoplasm within a delicate vascular network.

ICD-O code 8310/3

Synonym
The term "granular cell renal cell carcinoma" was used for many years for renal cell carcinomas with eosinophilic cytoplasm and high nuclear grade (1845). Some renal neoplasms of this morphology are now included among the clear cell type, but similar appearing cells occur in other tumour types, and so the term "granular cell renal cell carcinoma" should no longer be used. (2514). Historically, the terms Grawitz tumour and hypernephroma have also been used for clear cell renal cell carcinoma.

Macroscopy
Clear cell renal cell carcinomas (RCCs) are solitary and randomly distributed cortical tumours that occur with equal frequency in either kidney. Multicentricity and/or bilaterality occur in less than 5 percent of cases (1193). Multicentricity and bilaterality and early age of onset are typical of hereditary cancer syndromes such as von Hippel-Lindau syndrome. Clear cell RCCs are typically globular tumours which commonly protrude from the renal cortex as a rounded, bosselated mass. The interface of the tumour and the adjacent kidney is usually well demarcated, with a "pushing margin" and pseudocapsule. Diffuse infiltration of the kidney is uncommon. The average size is 7 cm in diameter but detection of small lesions is increasing in countries where radiologic imaging techniques are widely applied. Size itself is not a determinant of malignancy though increasing size is associated with a higher frequency of metastases. All kidney tumours of the clear cell type are considered malignant tumours. The clear cell renal cell carcinoma is typically golden yellow due to the rich lipid content of its cells; cholesterol, neutral lipids, and phospholipids are abundant. Cysts, necrosis, haemorrhage, and calcification are commonly present. Calcification and ossification occur within necrotic zones and have been demonstrated radiologically in 10 to 15 percent of tumours (209,822).

Tumour spread and staging
About 50% of clear cell RCCs are stage 1 and 2 and less than 5% stage 4. Invasion of perirenal and sinus fat and/or extension into the renal vein occurs in about 45% (1753). Recognition of stage pt3a requires detection of tumour cells in direct contact with perinephric or renal sinus fat. Clear cell RCCs most commonly metastasize hematogenously via the vena cava primarily to the lung, although lymphatic metastases also occur. Retrograde metastasis along the paravertebral veins, the v. testicularis/v. ovarii, intrarenal veins, or along the ureter may also occur. Clear cell RCC is well known for its propensity to metastasize to unusual sites, and late metastasis, even after ten years or more, is not uncommon. Prognosis of patients with clear cell RCC is most accurately predicted by stage. Within stages, grade has a strong predictive power. Although not formally part of the nuclear grading system, sarcomatoid change has a strongly negative effect, many of these patients dying in less than 12 months.

Histopathology
Clear cell RCC is architecturally diverse, with solid, alveolar and acinar patterns, the most common. The carcinomas typically contain a regular network of small thin-walled blood vessels, a diagnostically helpful characteristic of this tumour. No lumens are apparent in the alveolar pattern but a central, rounded luminal space filled with lightly acidophilic serous fluid or erythrocytes occurs in the
acinar pattern. The alveolar and acinar structures may dilate, producing microcystic and macrocystic patterns. Infrequently, clear cell renal cell carcinoma has a distinct tubular pattern and rarely a pseudopapillary architecture is focally present. The cytoplasm is commonly filled with lipids and glycogen, which are dissolved in routine histologic processing, creating a clear cytoplasm surrounded by a distinct cell membrane. Many tumours contain minority populations of cells with eosinophilic cytoplasm; this is particularly common in high grade tumours and adjacent to areas with necrosis or haemorrhage. In well preserved preparations, the nuclei tend to be round and uniform with finely granular, evenly distributed chromatin. Depending upon the grade, nucleoli may be inconspicuous, small, or large and prominent. Very large nuclei lacking nucleoli or bizarre nuclei may occasionally occur. A host of unusual histologic findings are described in clear cell renal cell carcinoma. Sarcomatoid change occurs in 5% of tumours and is associated with worse prognosis. Some tumours have central areas of fibromyxoid stroma, areas of calcification or ossification. Most clear cell RCCs have little associated inflammatory response; infrequently, an intense lymphocytic or neutrophilic infiltrate is present.

Immunoprofile
Clear cell RCCs frequently react with antibodies to brush border antigens, low molecular weight cytokeratins, CK8, CK18, CK19, AE1, Cam 5.2 and vimentin. High molecular weight cytokeratins, including CK14, and 34βE12 are rarely detected. The majority of clear cell RCCs react positively for renal cell carcinoma marker (1675), CD10 (140) and epithelial membrane antigen (776). MUC1 and MUC3 are consistently expressed (1479).

Grading
Nuclear grade, after stage, is the most important prognostic feature of clear cell renal cell carcinoma (441,764, 815,949,2433,2473,2940). The prognostic value of nuclear grade has been validated in numerous studies over the past 8 decades. Both 4-tiered and 3-tiered grading systems are in widespread use. The 4-tiered nuclear grading system (815) is as follows: Using the 10x objective, grade 1 cells have small hyperchromatic nuclei (resembling mature lymphocytes) with no visible nucleoli and little detail in the chromatin. Grade 2 cells have finely granular “open” chromatin but inconspicuous nucleoli at this magnification. For nuclear grade 3, the nucleoli must be easily unequivocally recognizable with the 10x objective. Nuclear grade 4 is characterized by nuclear pleomorphism, hyperchromasia and single to multiple macro-nucleoli. Grade is assigned based on the highest grade present. Scattered cells may be discounted but if several cells within a single high power focus have high grade characteristics, then the tumour should be graded accordingly.

Genetic susceptibility
Clear cell renal cell carcinoma constitutes a typical manifestation of von Hippel-Lindau disease (VHL) but may also occur in other familial renal cell cancer syndromes.

Somatic genetics
Although most clear cell RCCs are not related to von Hippel Lindau disease, 3p deletions have been described in the vast majority of sporadic clear cell renal cell carcinoma by conventional cytogenetic, FISH, LOH and CGH analyses. At least 3 separate regions on chromosome 3p have been implicated by LOH studies as relevant for sporadic renal cell carcinoma: one coincident with the von Hippel-Lindau (VHL) disease gene locus at 3p25-26, one at 3p21-22 and one at 3p13-14, which includes the chromosomal translocation point in familial human renal cell carcinoma. These data suggest involvement of multiple loci on chromosome 3 in renal cancer development. Mutations of the VHL gene have been described in 34-56% of sporadic clear cell RCC (307,792,897,2342,2400,2810). DNA methylation was observed in 19% of clear cell renal cell carcinomas. Therefore, somatic inactivation of the VHL gene may occur by allelic deletion, mutation, or epigenetic silencing in 70% or more. These data suggest that the VHL gene is the most likely candidate for a tumour suppressor gene in sporadic clear cell RCC.

Fig. 1.18 A VHL, renal carcinoma. Note clear cells and cysts. B Clear cell renal cell carcinoma. Typical alveolar arrangement of cells.
However, recent data give evidence for other putative tumour suppressor genes at 3p, e.g. RASSF1A at 3p21 (1789) and NRC-1 at 3p12 (1562). Chromosome 3p deletions have been observed in very small clear cell tumours of the kidney and are regarded as the initial event in clear cell cancer development (2107,2109,2925). Inactivation of the VHL gene has consequences for VHL protein function. The VHL protein negatively regulates hypoxia-inducible factor, which activates genes involved in cell proliferation, neo-vascularization, and extracellular matrix formation (642,1310,1828). Clonal accumulation of additional genetic alterations at many chromosomal locations then occurs in renal cancer progression and metastasis (247,339,958,1218,1754,2109,2179,2344,2345). High level gene amplifications are rare in clear cell renal cell carcinoma (1754). Individual chromosomal gains and losses have been analyzed for an association with patient prognosis. Chromosome 9p loss seems to be a sign of poor prognosis (1754,2341). Losses of chromosome 14q were correlated with poorer patient outcome, high histologic grade and high pathologic stage (226,1080,2344,2849). LOH on chromosome 10q around the PTEN/MAC locus have been frequently detected and were related to poor prognosis (2722). Expression levels of many genes have been studied in clear cell RCC. The role of p53 expression in renal cell carcinoma is controversial. A few studies suggest that p53 overexpression is associated with poor prognosis and with sarcomatoid transformation (1932,1939,2164,2659). High expression levels of bFGF, VEGF, IL-8, MMP-2, MMP-9, vimentin, MHC class II and E-cadherin may be important for development and/or progression (320,1472,1892,2391,2437). Expression of epidermal growth factor receptor (EGFR) is frequent in renal cell carcinoma and has been proposed as prognostic parameter (1755). Amplification of the EGFR gene on chromosome 7p13 is a major cause for EGFR expression in brain tumours, this pathway is uncommon in renal cell carcinoma (1756). HER2/neu amplifications are rare or absent in renal cell carcinoma (2339,2799). cDNA array analysis of clear cell renal carcinoma showed complex patterns of gene expression (1759,2887). It has been shown that the integration of expression profile data with clinical data could serve to enhance the diagnosis and prognosis of clear cell RCC (2551).
Multilocular cystic renal cell carcinoma

**Definition**
A tumour composed entirely of numerous cysts, the septa of which contain small groups of clear cells indistinguishable from grade 1 clear cell carcinoma.

**ICD-O code** 8310/3

**Clinical features**
There is a male:female predominance of 3:1. All have been adults (age range 20-76 years, mean = 51) [650]. No instance of progression of multilocular cystic renal cell carcinoma is known.

**Macroscopy**
While cysts are common in clear cell renal cell carcinomas, only rarely is the tumour entirely composed of cysts. In these tumours the number of carcinoma cells is small and diagnosis is challenging [1835]. In order to distinguish these tumours with excellent outcomes from other clear cell carcinomas, ones containing expansive nodules of carcinoma must be excluded and diagnosed simply as clear cell renal cell carcinoma [650]. Multilocular cystic renal cell carcinoma consists of a well-circumscribed mass of small and large cysts filled with serous or haemorrhagic fluid and separated from the kidney by a fibrous capsule. Diameters have ranged from 25 mm to 130 mm. More than 20% have calcification in the septa and osseous metaplasia occasionally occurs.

**Tumour spread and staging**
No tumour with these features has ever recurred or metastasized.

**Histopathology**
The cysts are usually lined by a single layer of epithelial cells or lack an epithelial lining. The lining cells may be flat or plump and their cytoplasm ranges from clear to pale. Occasionally, the lining consists of several layers of cells or a few small papillae are present [2561]. The nuclei almost always are small, spherical, and have dense chromatin. The septa consist of fibrous tissue, often densely collagenous. Within some of the septa there is a population of epithelial cells with clear cytoplasm. The epithelial cells resemble those lining the cysts and almost always have small dark nuclei. The clear cells form small collections but do not form expansile nodules. These epithelial cells often closely resemble histiocytes, or lymphocytes surrounded by retraction artefacts. Increased vascularity within the cell clusters is a clue to their nature.

**Immunoprofile**
The cells with clear cytoplasm in the septa frequently react strongly with antibodies to cytokeratins and epithelial membrane antigen and fail to react with antibodies to markers for histiocytes.
Papillary renal cell carcinoma

Definition
A malignant renal parenchymal tumour with a papillary or tubulopapillary architecture.

ICD-O code 8260/3

Epidemiology
Papillary renal cell carcinomas (PRCC) comprise approximately 10% of renal cell carcinoma in large surgical series (584,1860). The age and sex distribution of PRCC is similar to clear cell renal cell carcinoma with reported mean age at presentation and sex ratio (M:F) for large series ranging from 52-66 years and 1.8:1 to 3.8:1, respectively (76,584,587,1612).

Clinical features
Signs and symptoms are similar to clear cell renal cell carcinoma (1612). Radiological investigations are non-specific, although renal angiography studies have shown relative hypovascularity for PRCC (1860).

Macroscopy
PRCC frequently contains areas of haemorrhage, necrosis and cystic degeneration, and in well-circumscribed tumours an investing pseudocapsule may be identified (76,1612). Bilateral and multifocal tumours are more common in PRCC than in other renal parenchymal malignancies and in hereditary PRCC up to 3400 microscopic tumours per kidney have been described (1979,2169).

Histopathology
PRCC is characterized by malignant epithelial cells forming varying proportions of papillae and tubules. Tumour lined cysts with papillary excrescences may also be seen (585,1612,1860). The tumour papillae contain a delicate fibrovascular core and aggregates of foamy macrophages and cholesterol crystals may be present. Occasionally the papillary cores are expanded by oedema or hyalinized connective tissue (584,585). Solid variants of PRCC consist of tubules or short papillae resembling glomeruli (585,2173). Necrosis and haemorrhage is frequently seen and haemosiderin granules may be present in macrophages, stroma and tumour cell cytoplasm (1612). Calcified concretions are common in papillary cores and adjacent desmoplastic stroma, while calcium oxalate crystals have been reported (587,641,1612). Two morphological types of PRCC have been described (585): Type 1 tumours have papillae covered by small cells with scanty cytoplasm, arranged in a single layer on the papillary basement membrane. Type 2 tumour cells are often of higher nuclear grade with eosinophilic cytoplasm and pseudostratified nuclei on papillary cores. Type 1 tumours are more frequently multifocal. Sarcomatoid dedifferentiation is seen in approximately 5% of PRCC and has been associated with both type 1 and type 2 tumours (585).

Immunoprofile
Cytokeratin 7 (CK 7) expression has been reported for PRCC (831) however, this is more frequently observed in type 1 (87%) than type 2 (20%) tumours (585). Ultrastructural findings are not diagnostic and are similar to clear cell renal cell carcinoma (1888,2609).

Grading
There is no specific grading system for PRCC and the Fuhrman system (815) is accepted as applicable to both clear cell renal cell carcinoma and PRCC.

Table 1.04
Immunohistochemical profile of PRCC.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Number of cases</th>
<th>% showing positive expression</th>
</tr>
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<tbody>
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<td>AE1/AE3</td>
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<td>100</td>
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<tr>
<td>CAM 5.2</td>
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<td>100</td>
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</tr>
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</tr>
<tr>
<td>Ulex europeaus</td>
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</tr>
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</table>

From (140,585,831,1693,2169).

Fig. 1.25 Papillary renal cell carcinoma. A The papillary architecture is faintly visible in the friable tumour. B Gross specimen showing tumour haemorrhage and pseudoencapsulation. C Yellow streaks reflect the population of foamy macrophages.
Somatic genetics
Trisomy or tetrasomy 7, trisomy 17 and loss of chromosome Y are the commonest karyotypic changes in PRCC [1373]. High resolution studies have shown interstitial 3p loss of heterozygosity in some PRCC [1789,2723]. Trisomy of 12, 16 and 20 is also found in PRCC and may be related to tumour progression [618,1373], while loss of heterozygosity at 9p13 is associated with shorter survival [2340]. Comparative genomic hybridization studies show more gains of chromosomes 7p and 17p in type 1 PRCC when compared to type 2 tumours [1219], while more recently, differing patterns of allelic imbalance at 17q and 9p have been noted [2291].

Prognosis and predictive factors
In series of PRCC containing both type 1 and 2 tumours, five year survivals for all stages range from 49% to 84% [584,1612], with tumour grade [76, 675,1428,1753], stage at presentation [76,1753] and the presence of sarcomatoid dedifferentiation [76,1753] being correlated with outcome. Additionally the presence of extensive tumour necrosis and numerous foamy macrophages has been associated with a more favourable prognosis [76, 1612], while on multivariate modelling only tumour stage retained a significant correlation with survival [76]. While grade 1 tubulopapillary tumours between 0.5 and 2 cm are strictly defined as carcinomas, many pathologists prefer to report them as "papillary epithelial neoplasm of low malignant potential" for practical reasons. Up to 70% of PRCC are intrarenal at diagnosis [76,1428,1612,1860] and type 1 tumours are usually of lower stage and grade than type 2 tumours [76,585,587,1753]. Longer survivals have been demonstrated for type 1 when compared with type 2 PRCC on both univariate [1753] and multivariate analysis that included both tumour stage and grade [587].
Fig. 1.29 Papillary renal cell carcinoma. A Trisomy 7, 12, 13, 17 and 20 and deletion of 21 and Y. B Survival curves by grade for patients with papillary renal cell carcinoma. From C.M. Lohse et al. (1532).
Chromophobe renal cell carcinoma

Definition
Renal carcinoma characterized by large pale cells with prominent cell membranes.

ICD-O code 8317/3

Epidemiology
Chromophobe renal cell carcinoma (CRCC) accounts for approximately 5 per cent of surgically removed renal epithelial tumours. The mean age of incidence is in the sixth decade, with a range in age of 27-86 years, and the number of men and women is roughly equal. Mortality is less than 10% [512]. Sporadic and hereditary forms exist.

Clinical features
There are no specific signs and symptoms. On imaging, these are mostly large masses without necrosis or calcifications.

Macroscopy
Chromophobe renal cell carcinomas are solid circumscribed tumours with slightly lobulated surfaces. In unfixed specimens the cut surface is homogeneously light tan. Mortality is less than 10% [512]. Sporadic and hereditary forms exist.

Fig. 1.30 Chromophobe renal cell carcinoma (RCC). Typical homogeneously tan coloured tumour of the lower pole of the kidney.

Fig. 1.31 Chromophobe RCC. A Chromophobe cells are arranged along vascular channels. B Note chromophobe and eosinophilic cells.

Fig. 1.32 A Chromophobe RCC, eosinophilic variant. Note binucleated cells, perinuclear halos and tight intercellular cohesion. B Chromophobe RCC. Note typical granular cytoplasm with perinuclear clearance.
brown or tan turning light grey after formalin fixation.

**Tumour spread and staging**

The majority of CRCCs are stage T1 and T2 (86%) whereas only 10% show extension through the renal capsule into surrounding adipose tissue, only 4% show involvement of the renal vein (T3b) {512}. A few cases of lymph node and distant metastasis (lung, liver and pancreas) have been described {152,1635,2172}.

**Histopathology**

In general, the growth pattern is solid, sometimes glandular, with focal calcifications and broad fibrotic septa. In contrast to clear cell renal cell carcinoma, many of the blood vessels are thick-walled and eccentrically hyalinized. The perivascular cells are often enlarged. Chromophobe renal cell carcinoma is characterized by large polygonal cells with transparent slightly reticulated cytoplasm with prominent cell membranes. These cells are commonly mixed with smaller cells with granular eosinophilic cytoplasm. The eosinophilic variant of chromophobe carcinoma is purely composed of intensively eosinophilic cells with prominent cell membranes {2610}. The cells have irregular, often wrinkled, nuclei. Some are binucleated. Nucleoli are usually small. Perinuclear halos are common. Sarcomatoid transformation occurs {2047}. Another diagnostic hallmark is a diffuse cytoplasmic staining reaction with Hale’s colloidal iron stain {475,2608}.

**Immunoprofile**

Immunohistology presents the following antigen profile: pan-Cytokeratin+, vimentin-, EMA+ (diffuse), lectins+, parvalbumin+, RCC antigen-/+, CD10– {140,1635,1675,2513}.

**Ultrastructure**

Electron microscopically, the cytoplasm is crowded by loose glycogen deposits and numerous sometimes invaginated vesicles, 150-300 nm in diameter resembling those of the intercalated cells type b of the cortical collecting duct {722,2515}.

**Somatic genetics**

Chromophobe renal cell carcinomas are characterized by extensive chromosomal loss, most frequently -1,-2,-6,-10,-13,-17 and –21 {338,2464}. The massive chromosomal losses lead to a hypodiploid DNA index {42}. Endoreduplication/polyploidization of the hypodiploid cells has been observed. Telomeric associations and telomere shortening have also been observed {1113,1375}. At the molecular level, Contractor et al. {486} showed that there are mutations of...
TP53 tumour suppressor gene in 27% of the chromophobe RCCs. Sükösd et al. [2531] demonstrated loss of heterozygosity (LOH) around the PTEN gene at the 10q23.3 chromosomal region.

**Prognosis and predictive factors**
Sarcomatoid phenotype is associated with aggressive tumour growth and the development of metastasis.

---

**Fig. 1.37** Chromophobe renal cell carcinoma. A Electron micrograph showing the numerous cytoplasmic microvesicles and thick cytoplasmic membranes. B The perinuclear rarefaction and peripheral condensation of mitochondria responsible for the perinuclear halos.

**Fig. 1.38** Chromophobe renal cell carcinoma. Survival curves by grade for patients with chromophobe renal cell carcinoma. From C.M. Lohse et al. (1532).
Carcinoma of the collecting ducts of Bellini

Definition
A malignant epithelial tumour thought to be derived from the principal cells of the collecting duct of Bellini.

ICD-O code 8319/3

Synonym
Collecting duct carcinoma, Bellini duct carcinoma.

Epidemiology
Collecting duct carcinoma is rare, accounting for <1% of renal malignancies. Over 100 cases have been described and there is a wide age range from 13-83 years (mean, about 55) with a male to female ratio of 2:1 [2470].

Clinical features
Patients with collecting duct carcinoma usually present with abdominal pain, flank mass and haematuria. About one-third of patients have metastases at presentation. Metastases to bone are often osteoblastic. Upper tract imaging often suggests urothelial carcinoma and patients may occasionally present with positive urine cytology.

Macroscopy
Collecting duct carcinomas are usually located in the central region of the kidney. When small, origin within a medullary pyramid may be seen. Reported tumours range from 2.5 to 12 cm (mean, about 5 cm) and they typically have a firm grey-white appearance with irregular borders [2470]. Some tumours grow as masses within the renal pelvis. Areas of necrosis and satellite nodules may be present.

Tumour spread and staging
Collecting duct carcinomas often display infiltration of perirenal and renal sinus fat. Metastases to regional lymph nodes, lung, liver, bone and adrenal gland are common. Sometimes gross renal vein invasion is seen.

Histopathology
The diagnosis of collecting duct carcinoma is often difficult and to some extent is one of exclusion. While most collecting duct carcinomas are located centrally in the medullary zone, other common forms of renal cell carcinoma (clear cell, papillary) may also arise centrally from cortical tissue of the columns of Bertin. Criteria for diagnosing collecting duct carcinoma have been proposed [2470]. The prototypic collecting duct carcinoma has a tubular or tubulopapillary growth pattern in which irregular angulated glands infiltrate renal parenchyma and are associated with a desmoplastic stroma [775, 1298, 2262, 2470]. The edge of the tumour is often ill-defined and there is extensive permeation of renal parenchyma. Small papillary infoldings and micro-

Fig. 1.39 Carcinoma of the collecting ducts of Bellini.

Fig. 1.40 Carcinoma of the collecting ducts of Bellini. A Medullary location of the tumour. B Tubular type of growth. C Higher magnification discloses small papillary infoldings to the tubular lumina.
cystic change may be seen. Solid, cord-like patterns and sarcomatoid features may be encountered. The sarcomatoid change is a pattern of dedifferentiation similar to that seen in other types of renal carcinoma (153). The cells of collecting duct carcinoma usually display high grade (Fuhrman 3 and 4) nuclear features. The cells may have a hobnail pattern of growth and the cytoplasm is generally eosinophilic. Glycogen is usually inconspicuous in collecting duct carcinoma. Both intraluminal and intracytoplasmic mucin may be seen. Some tumours with other morphologies have been proposed as collecting duct carcinomas. The most frequent ones have a predominantly papillary growth pattern but they differ from usual papillary carcinoma by a lack of circumscription, broad stalks containing inflamed fibrous stroma, desmoplasia, high nuclear grade and sometimes an association with more typical tubular patterns of collecting duct carcinoma elsewhere (2470). The central location and associated tubular epithelial dysplasia (atypia) are helpful in supporting a diagnosis, although dysplasia may be seen in collecting ducts adjacent to other types of renal carcinoma.

**Immunoprofile**

Tumour cells usually display positivity for low molecular weight and broad spectrum keratins. High molecular weight keratins (34βE12, CK19) are commonly present and co-expression of vimentin may be seen (2470). There is variable immunostaining for CD15 and epithelial membrane antigen. The CD10 and villin stains are negative. Lectin histochemistry, usual *Ulex europaeus* agglutinin-1 and peanut lectin are commonly positive.

**Differential diagnosis**

The main differential diagnoses of collecting duct carcinoma include papillary renal cell carcinoma, adenocarcinoma or urothelial carcinoma with glandular differentiation arising in renal pelvis and metastatic adenocarcinoma (2470).

**Somatic genetics**

Molecular events that contribute to the development of collecting duct carcinomas (CDCs) are poorly understood because only few cases have been analyzed. LOH was identified on multiple chromosomal arms in CDC, including 1q, 6p, 8p, 13q, and 21q (2094). Loss of chromosomal arm 3p can be found in CDC (674,990). High density mapping of the entire long arm of chromosome 1 showed that the region of minimal deletion is located at 1q32.1-32.2 (2501). One study suggested that 8p LOH might be associated with high tumour stage and poor patient prognosis (2335). In contrast to clear cell RCC, HER2/neu amplifications have been described in CDCs (2357).

**Prognosis and predictive factors**

The typical collecting duct carcinomas have a poor prognosis with many being metastatic at presentation. About two-thirds of patients die of their disease within two years of diagnosis (2470).

---

**Table 1.05**

Diagnostic criteria for collecting duct carcinoma.

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Minor Criteria</th>
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<tbody>
<tr>
<td>- Location in a medullary pyramid (small tumours)</td>
<td>- Central location (large tumours)</td>
</tr>
<tr>
<td>- Typical histology with irregular tubular architecture and high nuclear grade</td>
<td>- Papillary architecture with wide, fibrous stalks and desmoplastic stroma</td>
</tr>
<tr>
<td>- Inflammatory desmoplastic stroma with numerous granulocytes</td>
<td>- Extensive renal, extrarenal, and lymphatic and venous infiltration</td>
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<tr>
<td>- Reactive with antibodies to high molecular weight cytokeratin</td>
<td>- Intra tubular epithelial atypia adjacent to the tumour</td>
</tr>
<tr>
<td>- Reactive with <em>Ulex europaeus</em> agglutinin lectin</td>
<td></td>
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<tr>
<td>- Absence of urothelial carcinoma</td>
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</table>

**Fig. 1.41** Carcinoma of the collecting ducts of Bellini. A Tubulopapillary type of growth. B,C Note high grade cytological atypia.
Renal medullary carcinoma

**Definition**
A rapidly growing tumour of the renal medulla associated almost exclusively with sickle cell trait.

**ICD-O code**  8319/3

**Epidemiology**
This is a rare tumour. Over a period of 22 years the Armed Forces Institute of Pathology had collected only 34 cases (562) and over the next 5 years only 15 more had been described (1304).

**Clinical features**

*Signs and symptoms*
With few exceptions these are seen in young people with sickle cell trait between ages 10 and 40 (mean age 22 years) and chiefly in males by 2:1. The common symptoms are gross haematuria and flank or abdominal pain. Weight loss and palpable mass are also common. Metastatic deposits such as cervical nodes or brain tumour may be the initial evidence of disease (2119).

*Imaging*
In the clinical setting of a young person with sickle cell trait it is often possible to anticipate the correct diagnosis with imaging studies (557,1304). Centrally located tumours with an infiltrative growth pattern, invading renal sinus, are typical. Caliectasis without pelviectasis and tumour encasing the pelvis are also described.

*Macroscopy*
These are poorly circumscribed tumours arising centrally in the kidney. Size ranges from 4 to 12 cm with a mean of 7 cm. Most show much haemorrhage and necrosis (562).

*Histopathology*
Most cases have poorly differentiated areas consisting of sheets of cells. A reticular growth pattern and a more compact adenoid cystic morphology are the common features. The cells are eosinophilic with clear nuclei and usually with prominent nucleoli. The sheets of cells can have squamoid or rhabdoid quality. Neutrophils are often admixed with the tumour and the advancing margins often bounded by lymphocytes. Oedematous or collagenous stroma forms a considerable bulk of many

![Fig. 1.42 Renal medullary carcinoma. Infiltrating tumour expanding renal contour.](image1)

![Fig. 1.43 Renal medullary carcinoma. Infiltrating tumour with perinephric extension at lower right.](image2)

![B](image3)

![C](image4)

![A](image5)

Fig. 1.42 Renal medullary carcinoma. Infiltrating tumour expanding renal contour.

Fig. 1.43 Renal medullary carcinoma. Infiltrating tumour with perinephric extension at lower right.

C.J. Davis
tumours. A majority of cases show droplets of cytoplasmic mucin and sickled erythrocytes (562).

**Immunoprofile**
Keratin AE1/AE3 is nearly always positive as is EMA but typically less strongly so. CEA is usually positive. One study found strong expression of low molecular weight cytokeratin (CAM 5.2) but negative high molecular weight cytokeratin (2220).

**Prognosis and predictive factors**
The prognosis is poor and the mean duration of life after surgery has been 15 weeks. Chemotherapy has been known to prolong survival by a few months (2084) but generally, this and radiotherapy has not altered the course of the disease (1304). Metastases are both lymphatic and vascular with lymph nodes, liver and lungs most often involved. These tumours are now widely regarded as a more aggressive variant of the collecting duct carcinoma (648,2470).
Renal carcinomas associated with Xp11.2 translocations / TFE3 gene fusions

Definition
These carcinomas are defined by several different translocations involving chromosome Xp11.2, all resulting in gene fusions involving the TFE3 gene.

Clinical features
These carcinomas predominantly affect children and young adults, though a few older patients have been reported [108]. The ASPL-TFE3 carcinomas characteristically present at advanced stage [109].

Macroscopy
Renal carcinomas associated with Xp11.2 translocations are most commonly tan-yellow, and often necrotic and haemorrhagic.

Histopathology
The most distinctive histopathologic appearance is that of a carcinoma with papillary architecture comprised of clear cells; however, these tumours frequently have a more nested architecture, and often feature cells with granular eosinophilic cytoplasm. The ASPL-TFE3 renal carcinomas are characterized by cells with voluminous clear to eosinophilic cytoplasm, discrete cell borders, vesicular chromat and prominent nucleoli. Psammoma bodies are constant and sometimes extensive, often arising within characteristic hyaline nodules [109]. The PRCC-TFE3 renal carcinomas generally feature less abundant cytoplasm, fewer psammoma bodies, fewer hyaline nodules, and a more nested, compact architecture [108].

Immunoprofile
The most distinctive immunohistochemical feature of these tumours is nuclear immunoreactivity for TFE3 protein [113]. Only about 50% express epithelial markers such as cytokeratin and EMA by immunohistochemistry [108,109], and the labeling is often focal. The tumours consistently label for the Renal Cell Carcinoma Marker antigen and CD10.

Ultrastructure
Ultrastructurally, Xp11.2-associated carcinomas most closely resemble clear cell renal carcinomas. Most of the ASPL-TFE3 renal carcinomas also demonstrate membrane-bound cytoplasmic granules and a few contain membrane-bound rhomboidal crystals identical to those seen in soft tissue alveolar soft part sarcoma (ASPS) [109]. Occasional PRCC-TFE3 renal carcinomas have demonstrated distinctive intracisternal microtubules identical to those seen in extraskeletal myxoid chondrosarcoma [108].

Somatic genetics
These carcinomas are defined by several different translocations involving chromosome Xp11.2, all resulting in gene fusions involving the TFE3 gene. These include the t(X;1)(p11.2;q21) [1710], which results in fusion of the PRCC (also known as RCC17 or ASPSCR1) and TFE3 genes [109,1056,1424], the t(X;1)(p11.2;p34), resulting in fusion of the PSF and TFE3 genes, and the inv(X)(p11;q12), resulting in fusion of the NonO (p54nrb) and TFE3 genes [471]. TFE3 is a member of the basic-helix-loop-helix family of transcription factors. Both the PRCC-TFE3 and ASPL-TFE3 fusion proteins retain the TFE3 DNA binding domain, localize to the nucleus, and can act as aberrant transcription factors [2432,2809], and (M. Ladanyi, unpublished observations). The expression levels of TFE3 fusion proteins appear aberrantly high compared to native TFE3 [113], perhaps because the fusion partners of TFE3 are ubiquitously expressed and contribute their promoters to the fusion proteins. Interestingly, while both the t(X;17) renal

Fig. 1.45 t(X:17) renal carcinoma. Note sheet like growth pattern and clear cells.

Fig. 1.46 t(X:17) renal carcinoma. Note papillary architecture, hyaline nodules and psammoma bodies. (A,B,C)

Renal carcinomas associated with Xp11.2 translocations / TFE3 gene fusions
carnomas and the soft tissue ASPS contain identical ASPL-TFE3 fusion transcripts, the t(X;17) translocation is consistently balanced (reciprocal) in the former but usually unbalanced in the latter (i.e. the derivative X chromosome is not seen in ASPS) [109].

**Prognosis and predictive factors**

Very little is known about the clinical behaviour of these carcinomas. While the ASPL-TFE3 renal carcinomas usually present at advanced stage, their clinical course thus far appears to be indolent.
Renal cell carcinoma associated with neuroblastoma

L.J. Medeiros

**Definition**
Renal cell carcinoma associated with neuroblastoma occurs in long-term survivors of childhood neuroblastoma.

**Etiology**
Therapy for neuroblastoma may play a role in the pathogenesis of subsequent RCC. However, one patient was not treated for stage IVS neuroblastoma, and a second patient developed RCC and neuroblastoma simultaneously [1380,1694]. A familial genetic susceptibility syndrome may be involved.

**Clinical features**
Eighteen cases have been reported. Males and females are equally affected. [1281,1380,1394,1489,1694,2743]. Age was <2 years at time of diagnosis of neuroblastoma. Median age at time of diagnosis of RCC was 13.5 years (range, 2 to 35).

**Macroscopy**
Either kidney may be involved and four cases were bilateral. Median tumour size, in 12 cases, was 4 cm (range, 1.0-8 cm).

**Tumour spread and staging**
Five patients developed metastases involving the liver, lymph nodes, thyroid and adrenal glands, and bone [1394,1694,2743].

**Histopathology**
These tumours are morphologically heterogeneous [1380]. Some tumours are characterized by solid and papillary architecture, cells with abundant eosinophilic cytoplasm with a lesser number of cells with reticular cytoplasm, and mild to moderate atypia [1281,1380,1694]. In a second group, the tumours are small, clear cell renal cell carcinomas that were detected incidentally.

**Immunoprofile**
These tumours are usually positive for EMA, vimentin and keratins 8, 18, and 20 and are negative for keratins 7, 14, and 19.

**Somatic genetics**
Cytogenetic analysis of two tumours showed deletions of multiple chromosomal loci [1380,1694]. Microsatellite analysis using polymorphic markers in three tumours showed allelic imbalances involving a number of loci, most often 20q13 [1281,1694,2743].

**Prognosis and predictive factors**
Prognosis correlates with tumour stage and the presence of high grade nuclear atypia, similar to other histologic types of RCC.

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**Fig. 1.50** Carcinoma associated with neuroblastoma. A Note a mixture of areas of compact growth resembling renal oncocytoma and areas of papillary growth. B Higher magnification showing nuclei of variable size, often with nucleoli of medium size. There is focal papillary architecture.

**Fig. 1.51** Carcinoma associated with neuroblastoma. A Conspicuous variability in nuclear size and shape. The architecture is papillary and there is a psammoma body. B Tumour composed of large cells with finely and coarsely granular eosinophilic cytoplasm. Some are vacuolated.
Mucinous tubular and spindle cell carcinoma

Definition
Low-grade polymorphic renal epithelial neoplasms with mucinous tubular and spindle cell features.

Epidemiology
There is a wide age range of 17-82 (mean 53) years and a male to female ratio of 1:4 (2024,2469).

Clinical features
They usually present as asymptomatic masses, often found on ultrasound. Occasionally, they may present with flank pain or hematuria.

Macroscopy
Macroscopically, mucinous tubular and spindle cell carcinomas, are well circumscribed and have grey or light tan, uniform cut surfaces.

Histopathology
Histologically, they are composed of tightly packed, small, elongated tubules separated by pale mucinous stroma. The parallel tubular arrays often have a spindle cell configuration sometimes simulating leiomyoma or sarcoma. Many of these tumours had been previously diagnosed as unclassified or spindle cell (sarcomatoid) carcinomas. Individual cells are small with cuboidal or oval shapes and low-grade nuclear features. Occasionally, areas of necrosis, foam cell deposits and chronic inflammation may be present. The mucinous stroma is highlighted with stains for acid mucins.

Immunoprofile
These tumours have a complex immunophenotype and stain for a wide variety of cytokeratins including low molecular weight keratins (CAM 5.2, MAK 6), CK7, CK18, CK19 and 34βE12 (2469). Epithelial membrane antigen is commonly present, and vimentin and CD15 staining may be seen. Markers of proximal nephron such as CD10 and villin are generally absent. These tumours show extensive positivity for Ulex europaeus, peanut and soya bean agglutinins.

Ultrastructure
The spindle cells show epithelial features like tight junctions, desmosomes, microvillous borders, luminal borders and occasional tonofilaments [2469].

Somatic genetics
Using comparative genomic hybridization and FISH, there is a characteristic combination of chromosome losses, generally involving chromosome 1, 4, 6, 8, 13 and 14 and gains of chromosome 7, 11, 16 and 17 (2137,2469).

Prognosis and predictive factors
The prognosis seems to be favourable; only one example has been reported with metastasis and this tumour is best considered as a low-grade carcinoma (2471).

Fig. 1.52 A, B, C Mucinous tubular and spindle cell carcinoma composed of spindle cells and cuboidal cells forming cords and tubules. Note basophilic extracellular mucin.
Papillary adenoma of the kidney

J.N. Eble
H. Moch

Definition
Papillary adenomas are tumours with papillary or tubular architecture of low nuclear grade and 5 mm in diameter or smaller.

ICD-O code 8260/0

Clinical features
Papillary adenomas are the most common neoplasms of the epithelium of the renal tubules. Autopsy studies have found papillary adenomas increase in frequency in adulthood from 10% of patients younger than 40 years to 40% in patients older than 70 years (653, 2163, 2854). Similar lesions frequently develop in patients on long-term hemodialysis and occur in 33% of patients with acquired renal cystic disease (1143).

Macroscopy
Papillary adenomas are well circumscribed, yellow to greyish white nodules as small as less than 1 mm in diameter in the renal cortex. Most occur just below the renal capsule. The smallest ones usually are spherical, but larger ones sometimes are roughly conical with a wedge-shaped appearance in sections cut at right angles to the cortical surface. Usually, papillary adenomas are solitary, but occasionally they are multiple and bilateral. When they are very numerous, this has been called “renal adenomatosis”.

Histopathology
Papillary adenomas have tubular, papillary, or tubulopapillary architectures corresponding closely to types 1 and 2 papillary renal cell carcinoma (585). Some have thin fibrous pseudocapsules. The cells have round to oval nuclei with stippled to clumped chromatin and inconspicuous nucleoli; nuclear grooves may be present. Mitotic figures usually are absent. In most, the cytoplasm is scant and pale, amphophilic to basophilic. Less frequently, the cytoplasm is voluminous and eosinophilic, resembling type 2 papillary renal cell carcinoma. Psammoma bodies are common, as are foamy macrophages (2161).

Somatic genetics
Loss of the Y chromosome and a combined trisomy of chromosome 7 and 17 are the first visible karyotype aberrations in papillary renal tumours. This combination of genetic alterations has been found as the sole karyotype change in small papillary renal tumours from 2 mm to 5 mm in diameter, all with nuclear grade 1 (1373). Based on these findings, it has been suggested that papillary adenomas acquire additional genetic alterations during growth, which change their biological behaviour (1369). One CGH analysis studied 6 papillary tumours less than 6 mm in diameter and observed gain of chromosome 7 in 4 specimens (2107). These data suggest that initiating genetic events for papillary renal adenomas include gains of chromosome 7 and loss of a sex chromosome. Small renal tumours demonstrate similar, but less extensive genetic alterations than their papillary renal carcinoma counterparts. The clinically indolent course of small papillary tumours may, in part, be a result of the lower number of genetic alterations per tumour. However, it is not possible to distinguish adenomas and carcinomas by genetic changes, because many carcinomas show only few genetic alterations.

Fig. 1.54 Papillary adenoma. A Two papillary adenomas in the renal cortex. These type 1 adenomas have complex papillae covered by a single layer of small epithelial cells with inconspicuous cytoplasm. B Papillary adenoma composed of complex branching papillae on partially hyalinized stromal cores.
Oncocytoma

Definition
Oncocytoma is a benign renal epithelial neoplasm composed of large cells with mitochondria-rich eosinophilic cytoplasm, thought to arise from intercalated cells.

ICD-O code 8290/0

Epidemiology
First described by Zippel in 1942 (2939) and later by Klein and Valensi (1335), oncocytoma comprises approximately 5% of all neoplasms of renal tubular epithelium in surgical series (77,453,563, 607,812,1060,1174,1497,2050,2178,2945). Most series show a wide age distribution at presentation with a peak incidence in the seventh decade of life. Males are affected nearly twice as often as females. Most occur sporadically.

Clinical features
Signs and symptoms
The majority is asymptomatic at presentation with discovery occurring during radiographic work-up of unrelated conditions. Few patients present with hematuria, flank pain, or a palpable mass.

Imaging
The diagnosis of oncocytoma may be suggested by computed tomography or magnetic resonance imaging in tumours featuring a central scar (558,1094).

Macroscopy
Oncocytomas are well-circumscribed, nonencapsulated neoplasms that are classically mahogany-brown and less often tan to pale yellow. A central, stellate scar may be seen in up to 33% of cases but is more commonly seen in larger tumours. Haemorrhage is present in up to 20% of cases but grossly visible necrosis is extremely rare (77,563,2050).

Histopathology
Characteristically, these tumours have solid compact nests, acini, tubules, or microcysts. Often there is a hypocellular-hyalinized stroma. The predominant cell type (so-called "oncocyte") is round-to-polygonal with densely granular eosinophilic cytoplasm, round and regular nuclei with evenly dispersed chromatin, and a centrally placed nucleolus. A smaller population of cells with scanty granular cytoplasm, a high nuclear cytoplasmic ratio, and dark hyperchromatic nuclei may also be observed. If microcysts are present, they may be filled with red blood cells. Occasional clusters of cells with pleomorphic and hyperchromatic nuclei are common. A rare oncocytoma may have one or two mitotic figures in the sections examined. Atypical mitotic figures are not seen. A few small foci of necroses do not exclude an oncocytoma. Isolated foci of clear cell change may be present in areas of stromal hyalinizations. While small papillae may very rarely be seen focally, pure or extensive papillary architecture is not a feature.
of this tumour. Microscopic extension into perinephric adipose tissue may be seen infrequently [1584] and vascular invasion has been described [77,563,2050]. Since oncocytomas are benign neoplasms, grading is not performed. There is no diffuse cytoplasmic Hale’s colloidal iron staining in oncocytomas.

Oncocytosis (Oncocytomatosis)
Several cases have been reported in which the kidneys have contained a large number of oncocytic lesions with a spectrum of morphologic features, including oncocytic tumours, oncocytic change in benign tubules, microcysts lined by oncocytic cells and clusters of oncocyes within the renal interstitium [1181,2618,2782]. The oncocytic nodules usually have the morphologic and ultrastructural features of oncocytoma although some may have either chromophobe or hybrid features.

Ultrastructure
Through ultrastructural examination, renal oncocytoma is characterized by cells containing numerous mitochondria, the majority of which are of normal size and shape, though pleomorphic forms are rarely seen [722,2617]. Other cytoplasmic organelles are sparse and unremarkable. Notably absent are the microvesicles typical of chromophobe tumours.

Somatic genetics
Most renal oncocytomas display a mixed population of cells with normal and abnormal karyotypes [1376,1378]. In a few oncocytomas, translocation of t(5;11)(q35;q13) was detected [513,826,1376,2108,2687]. Some of the cases show loss of chromosome 1 and 14 [1079,2108].

Prognosis and predictive factors
Renal oncocytomas are benign neoplasms. This conclusion is based largely on the data from several recent studies including rigorous pathologic review and adequate clinical follow-up in which not a single case of oncocytoma resulted in the death of a patient due to metastatic disease [77,563].

Renal cell carcinoma, unclassified

ICD-O code 8312/3
Renal cell carcinoma, unclassified is a diagnostic category to which renal carcinomas should be assigned when they do not fit readily into one of the other categories [1370,2514]. In surgical series, this group often amounts to 4-5% of cases. Since this category must contain tumours with varied appearances and genetic lesions, it cannot be defined in a limiting way. However, examples of features, which might place a carcinoma in this category include: apparent composites of recognized types, sarcomatoid morphology without recognizable epithelial elements, mucin production, mixtures of epithelial and stromal elements, and unrecognizable cell types. Sarcomatoid change has been found to arise in all of the types of carcinoma in the classification, as well as in urothelial carcinoma of the renal pelvic mucosa. Since there is no evidence that renal tumours arise de novo as sarcomatoid carcinomas, it is not viewed as a type of its own, but rather as a manifestation of high grade carcinoma of the type from which it arose. Occasionally, the sarcomatoid elements overgrow the antecedent carcinoma to the extent that it cannot be recognized; such tumours are appropriately assigned to renal cell carcinoma, unclassified.

Somatic genetics
Most renal oncocytomas display a mixed population of cells with normal and abnormal karyotypes [1376,1378]. In a few oncocytomas, translocation of t(5;11)(q35;q13) was detected [513,826,1376,2108,2687]. Some of the cases show loss of chromosome 1 and 14 [1079,2108].

Prognosis and predictive factors
Renal oncocytomas are benign neoplasms. This conclusion is based largely on the data from several recent studies including rigorous pathologic review and adequate clinical follow-up in which not a single case of oncocytoma resulted in the death of a patient due to metastatic disease [77,563].
Metanephric adenoma and metanephric adenofibroma

Definition
Metanephric adenoma is a highly cellular epithelial tumour composed of small, uniform, embryonic-appearing cells.

ICD-O codes
- Metanephric adenoma: 8325/0
- Metanephric adenofibroma: 9013/0
- Metanephric adenosarcoma: 8933/3

Epidemiology
Metanephric adenoma occurs in children and adults, most commonly in the fifth and sixth decades. There is a 2:1 female preponderance [561]. Patients with metanephric adenofibroma have ranged from 5 months to 36 years (median = 30 months) [120]. There is a 2:1 ratio of males to females. A single case of high grade sarcoma arising in association with metanephric adenoma (metanephric adenosarcoma) has been reported [2072].

Clinical features
Approximately 50% of metanephric adenoma are incidental findings with others presenting with polycythemia, abdominal or flank pain, mass, or hematuria. Presenting symptoms of metanephric adenofibroma have included polycythemia or hematuria; some have been incidental findings. Arroyo et al. [120] described several cases in which either Wilms tumour or carcinoma occurred in association with metanephric adenofibroma. Other than one patient with regional metastases from the carcinoma, these patients have had no progression.

Macroscopy
Metanephric adenomas range widely in size; most have been 30 to 60 mm in diameter [561]. Multifocality is uncommon. The tumours are typically well circumscribed but not encapsulated. The cut surfaces vary from grey to tan to yellow and may be soft or firm. Foci of haemorrhage and necrosis are common; calcification is present in approximately 20%, and small cysts in 10% [561,1237].

Metanephric adenofibromas are typically solitary tan partially cystic masses with indistinct borders [120].

Histopathology
Metanephric adenoma is a highly cellular tumour composed of tightly packed small, uniform, round acini with an embryonal appearance. Since the acini and their lumens are small, at low magnification this pattern may be mistaken for a solid sheet of cells. Long branching and angulated tubular structures also are common. The stroma ranges from inconspicuous to a loose oedematous stroma. Hyalinized scar and focal osseous metaplasia of the stroma are present in 10-20% of tumours [561]. Approximately 50% of tumours contain papillary structures, usually consisting of tiny cysts into which protrude blunt papillae reminiscent of immature glomeruli. Psammoma bodies are common and sometimes numerous. The junction with the kidney is usually sharp and without a pseudocapsule. The cells of metanephric adenoma are monotonous, with small, uniform nuclei and absent or inconspicuous nucleoli. The nuclei are only a little larger than those of lymphocytes and are round or oval with delicate chromatin. The cytoplasm is scant and pale or light pink. Mitotic figures are absent or rare.

Metanephric adenofibroma is a compos-
ite tumour in which nodules of epithelium identical to metanephric adenoma are embedded in sheets of moderately cellular spindle cells. The spindle cell component consists of fibroblast-like cells. Their cytoplasm is eosinophilic but pale and the nuclei are oval or fusiform. Nucleoli are inconspicuous and a few mitotic figures are present in a minority of cases. Variable amounts of hyalinization and myxoid change are present. Angiodysplasia and glial, cartilaginous, and adipose differentiation occur occasionally. The relative amounts of the spindle cell and epithelial components vary from predominance of spindle cells to a minor component of spindle cells. The border of the tumour with the kidney is typically irregular and the spindle cell component may entrap renal structures as it advances. The epithelial component consists of small acini, tubules and papillary structures, as described above in metanephric adenoma. Psammoma bodies are common and may be numerous.

**Immunoprofile**

Immunohistochemical studies of metanephric adenoma have given variable results. Positive reactions with a variety of antibodies to cytokeratins have been reported, as have positive reactions with antibody to vimentin (951). Positive intranuclear reactions with antibody to WT-1 are common in metanephric adenoma (1824). Epithelial membrane antigen and cytokeratin 7 are frequently negative and CD57 is positive.

The stroma of metanephric adenofibroma frequently reacts with antibody to CD34 (120). The reactions of the adenomatous elements are similar to those reported for metanephric adenoma.

**Somatic genetics**

Cytogenetic analysis of metanephric adenoma revealed normal karyotypes in 5 cases and normal copy numbers of chromosomes 7 and 17 were seen by FISH in 2 cases (840, 926, 1237, 2171, 2652). A deletion at chromosome 2p as the only genetic abnormality was described in 1 tumour (2522) and a tumour suppressor gene region on chromosome 2p13 was delineated (2058).
Metanephric stromal tumour

**Definition**
Metanephric stromal tumour is a rare benign paediatric renal neoplasm, which is identical to the stromal component of metanephric adenofibroma [110,1075].

**ICD-O code** 8935/1

**Clinical features**
Metanephric stromal tumour (MST) is approximately one-tenth as common as congenital mesoblastic nephroma [110,120]. The typical presentation is that of an abdominal mass, though haematuria is not uncommon and rare patients may present with manifestations of extra-renal vasculopathy such as hypertension or haemorrhage. Mean age at diagnosis is 24 months. A rare adult tumour has been identified [255].

**Macroscopy**
MST is typically a tan, lobulated fibrous mass centred in the renal medulla. Mean diameter is 5 cm. Approximately one-half of cases are grossly cystic, while one-sixth are multifocal.

**Histopathology**
MST is an unencapsulated but subtly infiltrative tumour of spindled to stellate cells featuring thin, hyperchromatic nuclei, and thin, indistinct cytoplasmic extensions. Many of the characteristic features of MST result from its interaction with entrapped native renal elements. MST characteristically surrounds and entraps renal tubules and blood vessels to form concentric 'onionskin' rings or collarettes around these structures in a myxoid background. More cellular, less myxoid spindle cell areas at the periphery of these collarettes yield nodular variations in cellularity. Most tumours induce angiodysplasia of entrapped arterioles, consisting of epithelioid transformation of medial smooth muscle and myxoid change. Rarely, such angiodysplasia...
results in intratumoral aneurysms. One-fourth of MSTs feature juxtaglomerular cell hyperplasia within entrapped glomeruli, which may occasionally lead to hypertension associated with hyper-reninism. One-fifth of MSTs demonstrate heterologous differentiation in the form of glia or cartilage. Necrosis is unusual, and vascular invasion is absent in MST.

**Immunoprofile**
MSTs are typically immunoreactive for CD34, but labeling may be patchy. Desmin, cytokeratins, and S-100 protein are negative, though heterologous glial areas label for GFAP and S-100 protein.

**Prognosis and predictive factors**
All identified MSTs have had a benign course, with no reports of metastases or even local recurrence as of this writing. Excision is adequate therapy. Rare patients have suffered morbidity or mortality from the manifestations of extra renal angiodysplasia, apparently induced by MST.

---

**Fig. 1.64** Metanephric stromal tumour. **A** Note spindled and epithelioid stromal cells and **(B)** striking angioplasia.

**Fig. 1.65** Metanephric stromal tumour. **A** Angiodysplasia and concentric perivascular growth. **B** CD34 positivity of spindle cells, predominantly away from entrapped tubules.

**Fig. 1.66** Metanephric stromal tumour. **A** Glial-epithelial complexes. **B** Note positivity for GFAP in glial foci.
Nephroblastoma

Definition
Nephroblastoma is a malignant embryonal neoplasm derived from nephrogenic blastemal cells that both replicates the histology of developing kidneys and often shows divergent patterns of differentiation.

ICD-O code 8960/3

Synonym
Wilms tumour.

Epidemiology
Nephroblastoma affects approximately one in every 8,000 children [317]. There is no striking sex predilection and tumours occur with equal frequency in both kidneys. The mean age at diagnosis is 37 and 43 months for males and females, respectively, and 96 percent of cases occur in individuals under 10 years of age, although presentation in adulthood has been reported [315,959, 1148]. The stable incidence of nephroblastoma in all geographic regions suggests that environmental factors do not play a major role in its development. The variation in incidence among different racial groups, however, indicates a genetic predisposition for this tumour is likely: the general risk is higher among African-Americans and lower among Asians.

Clinical features
Nephroblastoma most commonly comes to clinical attention due to the detection of an abdominal mass by a parent when bathing or clothing a child. Abdominal pain, hematuria, hypertension, and acute abdominal crisis secondary to traumatic rupture are also common. More rare presentations include anaemia, hypertension due to increased renin production, and polycythemia due to tumoural erythropoietin production [959,2087]. The majority of nephroblastomas are treated using therapeutic protocols created by either the International Society of Paediatric Oncology (SIOP) or the Children’s Oncology Group (COG). The SIOP protocols advocate preoperative therapy followed by surgical removal. This approach allows for tumour shrinkage prior to resection, yielding a greater frequency and ease of complete resectability. Continued therapy is then determined by the histologic evidence of responsiveness to therapy, as indicated by post-therapy classification. The COG (including the prior National Wilms Tumour Study Group) has long advocated primary resection of tumours, followed by therapy that is determined by stage and classification into "favourable" and "unfavourable" histology categories. This allows for greater diagnostic confidence and greater ability to stratify patients according to pathologic and biologic parameters. While the SIOP and COG protocols have intrinsically different philosophies regarding therapy, they have resulted in similar outcomes.

Imaging
Nephroblastoma typically manifests as a solid mass of heterogeneous appearance that distorts the renal parenchyma and collecting system. The lesion can be associated with foci of calcification. Isolated nephrogenic rests tend to appear as homogeneous nodules [1567].

Macroscopy
Most nephroblastomas are unicentric. However, multicentric masses in a single kidney and bilateral primary lesions have been observed in 7 and 5 percent of cases, respectively [492,2381,2820]. Nephroblastomas are usually solitary rounded masses sharply demarcated from the adjacent renal parenchyma by a capsule.

Table 1.06
Revised SIOP Working Classification of Nephroblastoma.

A. For pretreated cases
I. Low risk tumours
Cystic partially differentiated nephroblastoma
Completely necrotic nephroblastoma

II. Intermediate risk tumours
Nephroblastoma – epithelial type
Nephroblastoma – stromal type
Nephroblastoma – mixed type
Nephroblastoma – regressive type
Nephroblastoma – focal anaplasia

III. High risk tumours
Nephroblastoma – blastemal type
Nephroblastoma – diffuse anaplasia

B. For Primary nephrectomy cases
I. Low risk tumours
Cystic partially differentiated nephroblastoma

II. Intermediate risk tumours
Non-anaplastic nephroblastoma and its variants
Nephroblastoma-focal anaplasia

III. High risk tumours
Nephroblastoma – diffuse anaplasia

Fig. 1.67 Aniridia in a child, associated with nephroblastoma.
Nephroblastoma

peritumoural fibrous pseudocapsule. Lesions most commonly have a uniform, pale grey or tan appearance and a soft consistency, although they may appear firm and whorled if a large fraction of the lesion is composed of mature stromal elements. Polypoid protrusions of tumour into the pelvicaliceal system may occur resulting in a "botryoid" appearance (1602). Cysts may be prominent. Rarely, nephroblastoma occurs in extrarenal sites (28,1976).

Tumour spread and metastasis

Nephroblastomas generally have a restricted pattern of metastasis, most commonly regional lymph nodes, lungs, and liver (318). Metastatic sites other than these (i.e., bone or brain) are unusual and should suggest alternative diagnoses.

Table 1.07

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>I COG: Limited to kidney and completely resected. Renal capsule is intact. SIOP: Limited to kidney or surrounded with fibrous pseudocapsule if outside the normal contours of the kidney. Presence of necrotic tumour or chemotherapy-induced changes in the renal sinus or soft tissue outside the kidney does not upstage the tumour in the post-therapy kidney.</td>
<td></td>
</tr>
<tr>
<td>II COG &amp; SIOP: Renal sinus soft tissue may be minimally infiltrated, without any involvement of the sinus vessels. The tumour may protrude into the pelvic system without infiltrating the wall of the ureter. Intrarenal vessels may be involved. Fine needle aspiration does not upstage the tumour.</td>
<td></td>
</tr>
<tr>
<td>III COG &amp; SIOP: Gross or microscopic residual tumour confined to abdomen. Includes cases with any of the following: a) Involvement of specimen margins grossly or microscopically; b) Tumour in abdominal lymph nodes; c) Diffuse peritoneal contamination by direct tumour growth, tumour implants, or spillage into peritoneum before or during surgery; d) Residual tumour in abdomen e) Tumour removed non-contiguously (piecemeal resection) f) Tumour was surgically biopsied prior to preoperative chemotherapy. SIOP: The presence of necrotic tumour or chemotherapy-induced changes in a lymph node or at the resection margins should be regarded as stage III.</td>
<td></td>
</tr>
<tr>
<td>IV COG &amp; SIOP: Hematogenous metastases or lymph node metastasis outside the abdominopelvic region.</td>
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<tr>
<td>V COG &amp; SIOP: Bilateral renal involvement at diagnosis. The tumours in each kidney should be separately sub-staged in these cases.</td>
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</tbody>
</table>

Fig. 1.68 Nephroblastoma. A circumscribed, encapsulated lesion with cyst formation. B Polypoid extension into renal pelvis.

Staging

The most widely accepted staging systems for nephroblastomas rely on the identification of penetration of the renal capsule, involvement of renal sinus vessels, positive surgical margins, and positive regional lymph nodes; there are minor differences between the staging systems utilized by the SIOP and COG. While bilateral nephroblastomas are designated as stage V, their prognosis is determined by the stage of the most advanced tumour and by the presence or absence of anaplasia.

Histopathology

Nephroblastomas contain undifferentiated blastemal cells and cells differentiating to various degrees and in different proportions toward epithelial and stromal lineages. Triphasic patterns are the most characteristic, but biphasic and monophasic lesions are often observed. While most of these components represent stages in normal or abnormal nephrogenesis, non renal elements, such as skeletal muscle and cartilage occur (193). The blastemal cells are small, closely packed, and mitotically active rounded or oval cells with scant cytoplasm, and overlapping nuclei containing evenly distributed, slightly coarse chromatin, and small nucleoli. Blastemal cells occur in several distinctive patterns. The diffuse blastemal pattern is characterized by a lack of cellular cohesiveness and an aggressive pattern of invasion into adjacent connective tissues and vessels, in contrast to the typical circumscribed, encapsulated, and "pushing" border characteristic of most nephroblastomas. Other blastemal patterns tend to be cohesive. The nodular and serpentine blastemal patterns are characterized by round or undulating, sharply defined cords or nests of blastemal cells set in a...
loose fibromyxoid stroma.

An epithelial component of differentiation is present in most nephroblastomas. This pattern may be manifested by primitive rosette-like structures that are barely recognizable as early tubular forms; other nephroblastomas are composed of easily recognizable tubular or papillary elements that recapitulate various stages of normal nephrogenesis. Heterologous epithelial differentiation may occur, the most common elements being mucinous and squamous epithelium.

A variety of stromal patterns may occur and may cause diagnostic difficulty when blastemal and epithelial differentiation are absent. Smooth muscle, skeletal muscle and fibroblastic differentiation may be present. Skeletal muscle is the most common heterologous stromal cell type and large fields of the tumour often contain this pattern. Other types of heterologous stromal differentiation include adipose tissue, cartilage, bone, ganglion cells, and neuroglial tissue.

Post-chemotherapy changes

Chemotherapy induces necrosis, xanthomatos histiocytic foci, haemosiderin deposits and fibrosis. Other chemotherapy-induced changes include maturation of blastema, epithelial, and stromal components, with striated muscle being the most frequent. Remarkable responsiveness to chemotherapy has resulted in complete necrosis in some tumours; such cases are considered to be low risk and may receive minimal treatment after surgery [259]. In contrast, those tumours that do not show response to therapy have a reduced prognosis and increased requirement for therapy.

Anaplasia

Approximately 5% of nephroblastomas are associated with an adverse outcome and are recognized pathologically because of their “unfavourable” histology due to the presence of nuclear anaplasia [194,318,2952]. Anaplasia is rare during the first 2 years of life, and

Table 1.08

<table>
<thead>
<tr>
<th>Histologic criteria for focal anaplasia.</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Anaplasia must be circumscribed and its perimeter completely examined (May require mapping of anaplastic foci that extend to the edge of tissue sections)</td>
</tr>
<tr>
<td>- Anaplasia must be confined to the renal parenchyma</td>
</tr>
<tr>
<td>- Anaplasia must not be present within vascular spaces</td>
</tr>
<tr>
<td>- Absence of severe nuclear pleomorphism and hyperchromasia (severe “nuclear unrest”) in non-anaplastic tumour.</td>
</tr>
</tbody>
</table>

Fig. 1.69 Nephroblastoma. A Primitive epithelial differentiation. B Serpentine blastemal pattern.

Fig. 1.70 Nephroblastoma. A Skeletal muscle differentiation. B Cytologic appearance of blastemal cells.
increases in prevalence to approximately 13 percent by 5 years of age (934). Histologic diagnosis of anaplasia requires all of the following:

- Presence of multipolar polypliod mitotic figures. In order to qualify for anaplasia each component of the abnormal metaphase, must be as large, or larger, than a normal metaphase.

- Marked nuclear enlargement and hyperchromasia. The major dimensions of affected nuclei meeting the criteria are at least three times that of non-anaplastic nuclei in other areas of the specimen (2952). Nuclear enlargement should involve all diameters of the nucleus and should not be confused with simple elongation. The enlarged nucleus must also be hyperchromatic.

Anaplasia has been demonstrated to correlate with responsiveness to therapy rather than to aggressiveness. Non-responsiveness of anaplasia to chemotherapy explains why it is not obliterated by preoperative treatment and therefore may be detected at a somewhat increased frequency in post-therapy nephrectomy specimens (2759,2952). Accordingly, anaplasia is most consistently associated with tumour histology: areas of stromal differentiation and terminal epithelial differentiation show very low levels or no expression of WT-1, whereas areas of blastemal and early epithelial differentiation show high levels of WT-1 (415,965).

### Immunoprofile

The blastemal cells regularly express vimentin, and may also show focal expression of neuron specific enolase, desmin, and cytokeratin (690,786). Expression of WT-1 is not present in all nephroblastomas, and may be present in various other tumours. In nephroblastomas, it is confined to the nucleus and correlates with tumour histology: areas of stromal differentiation and terminal epithelial differentiation show very low levels or no expression of WT-1, whereas areas of blastemal and early epithelial differentiation show high levels of WT-1.

### Somatic genetics

Approximately 10% of nephroblastomas develop in association with one of several well-characterized dysmorphic syndromes (493,936). The WAGR syndrome (Wilms tumour, aniridia, genitourinary malformation, mental retardation) carries a 30% risk of developing nephroblastoma. These patients have a consistent deletion of chromosome 11p13 in their somatic cells involving the WT1 gene (362,860). WT1 encodes a zinc finger transcription factor that plays a major role in renal and gonadal development (981). Abnormalities involving WT1 are consistently found in the tumours of WAGR patients as well as in patients with Denys-Drash syndrome (a syndrome characterized by mesangial sclerosis, pseudohyperpladism, and a 90% risk of nephroblastoma). Patients with WAGR have deletions of WT1, whereas patients with Denys-Drash syndrome have constitutional inactivating point mutations in one copy of WT1 and their nephroblastomas show loss of the remaining normal
While WT1 alterations are strongly linked to the development of nephroblastoma in syndromic cases, their role in sporadic nephroblastoma is limited, with only one third of all nephroblastomas showing deletion at this locus and only 10% harbouring WT1 mutations. Beckwith-Wiedemann syndrome (characterized by hemihypertrophy, macroglossia, omphalocele, and visceromegaly) has been localized to chromosome 11p15, and designated WT2 although a specific gene has not been identified. Attempts to determine the precise genetic event at this locus has revealed the presence of a cluster of imprinted genes; whether or not a single gene is responsible for the increased risk for nephroblastoma remains unclear. The preferential loss of the maternal allele at this locus in cases of sporadic nephroblastoma suggests that genomic imprinting is involved in the pathogenesis of some tumours. Additional genetic loci are associated with familial nephroblastoma in patients with normal WT1 and WT2. Approximately 1 percent of patients with nephroblastoma have a positive family history for the same neoplasm. Most pedigrees suggest autosomal dominant transmission with variable penetrance and expressivity.

**Prognosis and predictive factors**
Most nephroblastomas are of low stage, have a favourable histology, and are associated with an excellent prognosis. A favourable outcome can be expected even among most neoplasms with small foci of anaplasia. The most significant unfavourable factors are high stage, and the presence of anaplasia. The majority of blastemal tumours are exquisitely sensitive to therapy. However, tumours that demonstrate extensive blastemal cells following therapy are associated with poor response to therapy and reduced survival. In SIOP protocols, these blastemal chemoresistant tumours are classified as "high risk" and are treated like anaplastic tumours.

### Table 1.10
Frequency of paediatric renal malignancies.

<table>
<thead>
<tr>
<th>Neoplasm</th>
<th>Estimated relative frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephroblastoma (nonanaplastic)</td>
<td>80</td>
</tr>
<tr>
<td>Nephroblastoma (anaplastic)</td>
<td>5</td>
</tr>
<tr>
<td>Mesoblastic nephroma</td>
<td>5</td>
</tr>
<tr>
<td>Clear cell sarcoma</td>
<td>4</td>
</tr>
<tr>
<td>Rhabdoid tumour</td>
<td>2</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>4</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td></td>
</tr>
<tr>
<td>Peripheral neuroectodermal tumour</td>
<td></td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td></td>
</tr>
<tr>
<td>Renal carcinoma</td>
<td></td>
</tr>
<tr>
<td>Angiomyolipoma</td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td></td>
</tr>
<tr>
<td>Other rare neoplasms</td>
<td></td>
</tr>
</tbody>
</table>

WT1 allele [2043].
Nephrogenic rests and nephroblastomatosis

**Definition**
Nephrogenic rests are abnormally persistent foci of embryonal cells that are capable of developing into nephroblastomas. Nephroblastomatosis is defined as the presence of diffuse or multifocal nephrogenic rests. Nephrogenic rests are classified into perilobar (PLNR) and intralobar (ILNR) types.

**Epidemiology**
Nephrogenic rests are encountered in 25% to 40% of patients with nephroblastoma, and in 1% of infant autopsies [190,192, 195,210,303].

**Histopathology**
PLNRs and ILNRs have a number of distinguishing structural features.

*Perilobar nephrogenic rests*
PLNRs are sharply circumscribed and located at the periphery of the renal lobe. A PLNR may be dormant or may have several other fates: most commonly the rest will regress with peritubular scarring resulting in an obsolescent rest. PLNR may also undergo active proliferative overgrowth, resulting in hyperplastic nephrogenic rests, which can be almost impossible to distinguish from nephroblastoma. Rarely, PLNRs form a band around the surface of the kidney resulting in massive renal enlargement, (diffuse hyperplastic perilobar nephroblastomatosis). Nephroblastoma developing within a PLNR is recognized by its propensity for spherical expansile growth and a peritumoral fibrous pseudocapsule separating

---

**Table 1.11**
Features distinguishing perilobar from intralobar rests.

<table>
<thead>
<tr>
<th></th>
<th>Perilobar rests</th>
<th>Intralobar rests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Position in lobe</td>
<td>Peripheral</td>
<td>Random</td>
</tr>
<tr>
<td>Margins</td>
<td>Sharp, demarcated</td>
<td>Irregular, intermingling</td>
</tr>
<tr>
<td>Composition</td>
<td>Blastema, tubules, Stroma scant or sclerotic</td>
<td>Stroma, blastema, tubules, Stroma often predominates</td>
</tr>
<tr>
<td>Distribution</td>
<td>Usually multifocal</td>
<td>Often unifocal</td>
</tr>
</tbody>
</table>

---

**Fig. 1.72** Diffuse hyperplastic perilobar nephroblastomatosis (upper pole) with two spherical nephroblastomas and an separate perilobar nephrogenic rest in lower pole.

**Fig. 1.73** Perilobar nephrogenic rest. Note well demarcated, lens shaped subcapsular collection of blastemal and tubular cells.
the neoplasm from the adjacent rest and normal kidney.

**Intralobar nephrogenic rests**

In contrast to PLNRs, ILNRs are typically located in the central areas of the lobe, are poorly circumscribed and composed of stromal elements as well as epithelial tubules. Like PLNRs, ILNRs may be dormant, regress, or undergo hyperplasia. Nephroblastoma developing with ILNRs are often separated from the underlying rest by a peritumoural fibrous pseudocapsule.

**Prognosis and predictive factors**

In diffuse hyperplastic nephroblastomatosis, the risk for the development of nephroblastoma is extraordinarily high. Chemotherapy is commonly utilized because it reduces the compressive burden of nephroblastic tissue, which enables normalization of renal function, and reduces the number of proliferating cells that may develop a clonal transformation. There is a high risk of developing multiple nephroblastomas as well as anaplastic nephroblastomas. Therefore, their tumours must be carefully watched and monitored for responsiveness to therapy.

In the management of patients with nephroblastomatosis, imaging screening by serial ultrasonography and CT scans enables an early detection of nephroblastoma [191]. Prompt therapy can minimize the amount of native kidney that requires surgical excision (nephron sparing approach), thereby maximizing the preservation of renal function.

**Fig. 1.74** Hyperplasia within a large perilobar nephrogenic rest.

**Fig. 1.75** Intralobar nephrogenic rest. A Ill defined proliferation of embryonal cells and intermingling with the native kidney. B Hyperplastic blastemal cells proliferating within the rest intermingling with the native kidney.
Cystic partially differentiated nephroblastoma

Definition
Cystic partially differentiated nephroblastoma is a multilocular cystic neoplasm of very young children, composed of epithelial and stromal elements, along with nephroblastosomatous tissue.

ICD-O code 8959/1

Rarely, Wilms tumour may be composed entirely of cysts with delicate septa. Within the septa are small foci of blastema, immature-appearing stromal cells, and primitive or immature epithelium. Such tumours are called "cystic partially differentiated nephroblastoma" (329,1249). When no nephroblastosomatous elements are found, the term "cystic nephroma" has been applied although it is recognized that these lesions are not the same as the morphologically similar ones which occur in adults (646,650). Cystic partially differentiated nephroblastoma occurs with greater frequency in boys than in girls; almost all patients are less than 24 months old, and surgery is almost always curative (592, 1250,1251). Joshi and Beckwith reported one recurrence, possibly a complication of incomplete resection (1250).

The tumours often are large, particularly considering the patient’s age, ranging up to 180 mm in diameter. Cystic partially differentiated nephroblastoma is well circumscribed from the remaining kidney by a fibrous pseudocapsule and consists entirely of cysts of variable size. The septa are thin and there are no expansile nodules to alter the rounded contour of the cysts. The cysts in cystic partially differentiated nephroblastoma and are lined with flattened, cuboidal, or hobnail epithelium, or lack lining epithelium (1249). The septa are variably cellular and contain undifferentiated and differentiated mesenchyme, blastema, and nephroblastomatous epithelial elements (1249). Skeletal muscle and myxoid mesenchyme are present in the septa of most tumours. Cartilage and fat are present occasionally (1250,1251). Focally, the septal elements may protrude into the cysts in microscopic papillary folds, or gross polyps in the papillonodular variant of cystic partially differentiated nephroblastoma. The epithelial components consist mainly of mature and immature microscopic cysts resembling cross sections of tubules and stubby papillae resembling immature glomeruli.

Fig. 1.77 Cystic partially differentiated nephroblastoma. A The septa of cystic partially differentiated nephroblastoma often contain aggregates of blastema. B Pericystic part of the tumour contains immature epithelial elements forming short papillae reminiscent of fetal glomeruli.

Fig. 1.76 Cystic partially differentiated nephroblastoma forms a well-circumscribed mass composed entirely of small and large cysts.
Clear cell sarcoma

Definition
Clear cell sarcoma of the kidney (CCSK) is a rare paediatric renal sarcoma with a propensity to metastasize to bone.

ICD-O code 9044/3

Clinical features
CCSK comprises approximately 3% of malignant paediatric renal tumours. CCSK is not associated with Wilms tumour-related syndromes or nephrogenic rests. The male to female ratio is 2:1. The mean age at diagnosis is 36 months. The frequency of osseous metastases led to the proposed name "bone metastasizing renal tumour of childhood".

Macroscopy
CCSKs are typically large (mean diameter 11 cm) and centred in the renal medulla, and always unicentric. CCSK are unencapsulated but circumscribed, tan, soft, and mucoid, and almost always focally cystic.

Histopathology
The classic pattern of CCSK features nests or cords of cells separated by regularly spaced, arborizing fibrovascular septa. The cord cells may be epithelioid or spindled, and are loosely separated by extracellular myxoid material that mimics clear cytoplasm. Nuclei are round to oval shaped, have fine chromatin, and lack prominent nucleoli. The septa may be thin, regularly branching "chicken-wire" capillaries, or thickened sheaths of fibroblastic cells surrounding a central capillary. While CCSKs are grossly circumscribed, they characteristically have subtly infiltrative borders, entrapping isolated native nephrons. CCSK has varied histopathologic pat-
Pools of acellular hyaluronic acid lead to the myxoid pattern (781), while hyaline collagen simulating osteoid characterizes the sclerosing pattern. A cellular pattern mimics other paediatric small round blue cell tumours, whereas epithelioid (trabecular or pseudoacinar) patterns may mimic Wilms tumour. Prominent palisaded, spindled and storiform patterns mimic other sarcomas. Approximately 3% of CCSKs are anaplastic. Post-therapy recurrences may adopt deceptively-bland appearances simulating fibromatosis or myxoma (114,781).

**Immunoprofile / Ultrastructure**

While vimentin and BCL2 are typically reactive, CCSK is uniformly negative with CD34, S100 protein, desmin, MIC2 (CD99), cytokeratin, and epithelial membrane antigen (114). The cord cells of CCSK have a high nucleus/cytoplasm ratio, with thin cytoplasmic extensions surrounding abundant extracellular matrix. The cytoplasm has scattered intermediate filaments (980).

**Prognosis and predictive factors**

The survival of patients with CCSK has increased from only 20% up to 70% due in large part to the addition of adriamycin (doxorubicin) to chemotherapeutic protocols (114,935). Nonetheless, metastases may occur as late as 10 years after initial diagnosis. While involvement of perirenal lymph nodes is common at diagnosis (29% of cases), bone metastases are the most common mode of recurrence (1628,1629). CCSK is also distinguished from Wilms tumour by its proclivity to metastasize to unusual sites such as (in addition to bone) brain, soft tissue, and the orbit.

**Immunoprofile / Ultrastructure**

While vimentin and BCL2 are typically reactive, CCSK is uniformly negative with CD34, S100 protein, desmin, MIC2 (CD99), cytokeratin, and epithelial membrane antigen (114). The cord cells of CCSK have a high nucleus/cytoplasm ratio, with thin cytoplasmic extensions surrounding abundant extracellular matrix. The cytoplasm has scattered intermediate filaments (980).

**Prognosis and predictive factors**

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Rhabdoid tumour

**Definition**
Rhabdoid tumour of the kidney (RTK) is a highly invasive and highly lethal neoplasm of young children composed of cells with vesicular chromatin, prominent nucleoli, and hyaline intracytoplasmic inclusions.

**ICD-O code** 8963/3

**Epidemiology**
Rhabdoid tumour comprises approximately 2% of all paediatric renal tumours. The mean age at diagnosis is approximately 1 year, and approximately 80% of patients are diagnosed in the first 2 years of life. The diagnosis is highly suspect over the age of 3, and virtually nonexistent over the age of 5. Most previously reported RTKs over the age of 5 have subsequently proven to be renal medullary carcinomas [2795].

**Clinical features**
The most common presentation is that of haematuria. A significant number of patients present with disseminated disease. Approximately 15% of patients will develop a tumour of the posterior fossa of the brain that resembles PNET morphologically.

**Macroscopy**
Tumours are typically large, haemorrhagic and necrotic, with ill-defined borders that reflect its highly invasive nature.

**Histopathology**
These tumours are unencapsulated, and feature sheets of tumour cells that aggressively overrun native nephrons. Vascular invasion is usually extensive. Tumour cells characteristically display the cytologic triad of vesicular chromatin, prominent cherry-red nucleoli, and hyaline pink cytoplasmic inclusions. A subset of tumours may be composed predominantly of primitive undifferentiated small round cells, but on closer inspection small foci of cells with diagnostic cytologic features can be identified.

**Immunoprofile**
Nonspecific trapping of antibodies by the whorled cytoplasmic inclusions can give a wide range of false positive results. The most consistent and characteristic finding is that of strong vimentin labeling and focal but intense labeling for EMA.

**Ultrastructure**
The cytoplasmic inclusions correspond to whorls of intermediate filaments having a diameter of 8 to 10 nm.

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**Fig. 1.82** Rhabdoid tumour. CT showing large focal cystic tumour (left).

**Fig. 1.83** Rhabdoid tumour showing extensive tumour necrosis and haemorrhage.

**Fig. 1.84 A, B** Rhabdoid tumour of the kidney. The nucleus is vesiculated. The cytoplasm contains eosinophilic inclusions.
Somatic genetics
Biallelic inactivation of the hSNF5/INI1 tumour suppressor gene, which resides on the long arm of chromosome 22, is the molecular hallmark of RTK [242,2729]. Inactivation of this gene is also seen in morphologically similar rhabdoid tumours which occur in the soft tissue, brain, and occasionally other visceral sites. All of these tumours typically affect young children, and are usually lethal. The hSNF5/INI1 gene encodes a protein involved in chromatin remodeling that is thought to regulate the accessibility of transcription factors to DNA, and its inactivation is thought to promote neoplasia by altering gene expression secondary to its effect upon chromatin structure. Inactivation occurs via mutation, deletion or whole chromosome loss, accounting for the frequent cytogenetic finding of monosomy 22 in these neoplasms. Children with concurrent RTK and PNET-like tumours of the posterior fossa of the CNS frequently harbour germline mutations in the hSNF5/INI1 gene [241]. Inactivation of the second allele has been shown to occur by different mechanisms in these patients’ two cancers, confirming the clinicopathologic impression that these are independent neoplasm [790,2311]. A familial “rhabdoid predisposition syndrome” encompassing renal and extrarenal rhabdoid tumours has been described in which affected family members harbour constitutional inactivation of hSNF5/INI1 [2368,2588].

Prognosis and predictive factors
Outcome is typically dismal, as over 80% of patients will die of tumour within 2 years of diagnosis. The rare patients who present with tumour confined to the kidney may have a slightly better prognosis.
**Congenital mesoblastic nephroma**

**Definition**
Congenital mesoblastic nephroma (CMN) is a low-grade fibroblastic sarcoma of the infantile kidney and renal sinus.

**ICD-O code** 8960/1

**Clinical features**
CMN comprises two percent of paediatric renal tumours [193,1845]. CMN is the most common congenital renal neoplasm, and ninety percent of cases occur in the first year of life. The typical presentation is that of an abdominal mass.

**Macroscopy**
Classic CMN has a firm, whorled texture, while cellular CMN are more typically soft, cystic and haemorrhagic.

**Histopathology**
Classic CMN (24% of cases) is morphologically identical to infantile fibromatosis of the renal sinus [265]. Tumours are composed of interlacing fascicles of fibroblastic cells with thin tapered nuclei, pink cytoplasm, low mitotic activity, and an abundant collagen deposition. The tumour dissects and entraps islands of renal parenchyma. Cellular CMN (66% of cases) is morphologically identical to infantile fibrosarcoma. These tumours have a pushing border, and are composed of poorly formed fascicles, which give way to sheet-like growth patterns. The tumour shows a high mitotic rate, and frequently features necrosis. Mixed CMN (10% of cases) has features of both classic and cellular CMN within the same tumour.

**Immunoprofile**
These tumours are immunoreactive for vimentin and often actin with desmin reactivity being rare and CD34 being absent. Ultrastructurally, tumours have features of myofibroblasts or fibroblasts.

**Somatic genetics**
While classic CMNs are typically diploid, cellular CMNs frequently feature aneuploidy of chromosomes 11, 8, and 17 [1377,2063,2338]. Cellular CMN but not classic CMN demonstrates a specific chromosome translocation, t(12;15)(p13;q25), which results in a fusion of the ETV6 and NTRK3 genes [1336,2255]. Interestingly, the same chromosome translocation and gene fusion present in cellular CMN was first identified in infantile fibrosarcoma, and is not present in infantile fibromatosis [1337]. Hence, the analogy between cellular CMN and infantile fibrosarcoma, and between classic CMN and infantile fibromatosis, appears appropriate.

The oncogenic mechanism of the ETV6-NTRK3 gene fusion remains to be determined. ETV6 is an ETS transcription factor previously implicated in translocations in paediatric B-cell acute lymphoblastic leukaemia. NTRK3 is a tyrosine kinase receptor that responds to extracellular signals. ETV6-NTRK3 fusion transcripts encode a chimeric protein in which the sterile-alpha-motif (SAM) protein dimerization domain of the ETV6...
transcription factor is fused to the protein tyrosine kinase (PTK) of NTRK3. ETV6-NTRK3 (EN) has potent transforming activity in murine fibroblasts, which is mediated by ligand-independent homodimerization through the SAM domain and activation of the PTK domain. This in turn constitutively activates two major effector pathways of wild-type NTRK3, namely the Ras-MAP kinase (MAPK) mitogenic pathway and the phosphatidylinositol-3-kinase (PI3K)-AKT pathway mediating cell survival, and both are required for EN transformation \((1516,2621,2764)\). Virtually all congenital fibrosarcoma and cellular CMN cases expressing ETV6-NTRK3 also have trisomy 11 \((1336,1337)\). One intriguing possibility is that trisomy 11 provides cells with an additional copy of the 11p15.5 gene \((IGF2)\) encoding the insulin-like growth factor \((IGF)\)-2 anti-apoptotic factor \((178)\). IGF2 binds to the insulin-like growth factor 1 receptor, which was recently shown to be essential for EN transformation \((1788)\).

**Prognosis and predictive factors**

When completely excised, CMN is associated with an excellent prognosis. Five percent of patients develop recurrence, which is related to the incompleteness of resection and not to whether the tumour was of cellular or classic type. Only rare cases of hematogenous metastases and tumour related deaths have been reported \((1051,2758)\).

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**Fig. 1.90** Congenital mesoblastic nephroma. A Mixed type. Note that the left half is identical to classic type and the right half is identical to the cellular type. B Classic type. Note fascicles of fibroblastic cells adjacent to native renal tubules, which show embryonal hyperplasia. C Classic type. Note fascicles of fibroblastic cells resembling fibromatosis dissecting the native kidney.
Ossifying renal tumour of infancy

**Definition**
Ossifying renal tumour of infancy (ORTI) is an intracalyceal mass composed of osteoid trabeculae, osteoblast-like cells and a spindle cell component, arising from, and attached to the medullary pyramid.

**ICD-O code** 8967/0

ORTI is extremely rare, only 12 cases have been reported in the English literature [414,1184,2462,2715]. Males predominate (9/12). Age at presentation was 6 days to 17 months.

The exact nature of ORTI spindle cells is still uncertain. No cases have been reported in association with Wilms tumour or with WT1/WT2 gene syndromes on chromosome 11p.

All cases presented with gross haematuria except one which manifested as a palpable abdominal mass. Calcification of the tumour frequently suggests renal calculus.

ORTI is grossly well circumscribed and measures 1-6 cm in diameter.

Microscopically, there is a characteristic coarse trabecular osteoid meshwork with interspersed large cuboidal osteoblast-like cells that express EMA as well as vimentin, but not cytokeratin. Sheets of uniform spindle cells with ovoid nuclei may entrap renal tubules.

The outcome has been uniformly benign and conservative surgical management is recommended.

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Haemangiopericytoma

**ICD-O code** 9150/1

Less than 30 primary renal haemangiopericytomas are reported in the literature [788,1715,1992]. Most of them arise in the renal sinus and the perirenal tissue. There are no specific radiological features. Paraneoplastic syndromes, like hypoglycemia or hypertension, may occur. These tumours are large, firm and histologically composed of a proliferation of fusiform pericytes separated by numerous capillaries presenting a staghorn configuration. Immunohistochemically, the tumour cells are positive for CD34, negative for CD31, actin and CD99. Behaviour of haemangiopericytoma is difficult to predict. Late recurrence or metastases can never be excluded, especially when the tumour size is over 5 centimeters and mitotic rate over 4 per 10 HPF. Some haemangiopericytomas of the literature could be reevaluated as solitary fibrous tumours [1595]. These two entities share almost the same histological pattern and the same imprecise potential of malignancy.
Leiomyosarcoma

Definition
A leiomyosarcoma is a malignant neoplasm demonstrating smooth muscle differentiation.

ICD-O code 8890/3

Epidemiology
Although leiomyosarcoma is a rare primary renal neoplasm, it is the most common renal sarcoma accounting for 50-60% of cases [950,2742]. Most occur in adults, and men and women are equally affected.

Clinical features
Patients usually present with flank pain, haematuria and a mass. Leiomyosarcoma is aggressive with a 5-year survival rate of 29-36%; most patients die of disease within 1-year of diagnosis. It metastasizes to lung, liver, and bone. Irradiation and chemotherapy are ineffective, therefore, complete surgical extirpation is the only therapy. Small size (< 5 cm), low histological grade, and renal-limited disease are associated with the most favourable outcome.

Macroscopy
Leiomyosarcoma may arise from the renal capsule, renal parenchyma, pelvic muscularis, or the main renal vein [273,274, 306,950,1816,1919,2742]. Tumours arising in the capsule or parenchyma cannot be distinguished from other renal cortical neoplasms by imaging studies. Pelvic leiomyosarcoma may be regarded as a transitional cell carcinoma until microscopic examination is performed.

Histopathology
Leiomyosarcomas are spindle cell lesions with a fascicular, plexiform, or haphazard growth pattern. Low grade lesions resemble smooth muscle cells, but high grade lesions are pleomorphic and undifferentiated, requiring immunohistochemical stains to separate from other sarcomas, the more common sarcomatoid carcinomas, and from atypical forms of epithelioid angioleiomyolipoma [274]. Necrosis, nuclear pleomorphism, and more than a rare mitotic figure indicate malignancy.

Osteosarcoma

ICD-O code 9180/3

Primary osteosarcoma of the kidney is an exceedingly rare neoplasm with less than 20 cases reported in the literature [1716,2800,]. Pathogenesis of these tumours remains unclear and their relationship with carcinomas may be suggested. Compared to osteosarcoma of bone, it occurs in older patients, of over 40 years of age. The male/female ratio is roughly equal. Clinically, there are no specific symptoms. Nearly all the tumours exhibit a high stage (T3 or T4) at time of diagnosis. Early local recurrence and/or metastatic spread (especially pulmonary) are frequently observed. Histologically, primary renal osteosarcoma shows a pleomorphic pattern and consists of spindle and multinucleated giant tumour cells producing neoplastic osteoid and bone. The prognosis of primary renal osteosarcoma is very poor despite aggressive therapeutic approach combining radical surgery, radiotherapy and polychemotherapy.
Renal angiosarcoma

**Definition**
Primary renal angiosarcomas are exceedingly rare aggressive tumours of endothelial cells.

**ICD-O code** 9120/3

**Synonym**
Haemangiosarcoma.

**Epidemiology**
About 23 cases of this tumour have been documented [396,1096,1447,1502]. The mean age is 58 years (range 30 to 77 years). The etiology is unknown. An androgen factor has been discussed because of a strong male predominance (ratio 19:4) and experimental data [420].

**Localization and clinical features**
Primary renal angiosarcomas occur near the renal capsule. Clinical symptoms are flank pain, haematuria, palpable tumour and weight loss.

**Macroscopy**
Grossly, the tumours consist of ill-defined, haemorrhagic spongy masses.

**Histopathology**
Microscopically, they show the same changes that characterize other angiosarcomas. The tumour cells are spindle-shaped, rounded or irregular in outline with hyperchromatic and elongated or irregular nuclei. Bizarre nuclei and multinucleated cells may be seen. Mitotic figures are frequently identified. Poorly differentiated areas are composed of large sheets of spindled or epithelioid cells that are difficult to distinguish from other sarcomas or carcinomas. Some areas may reveal well-differentiated neoplastic capillary-size vessels comparable to haemangiomas or less well-differentiated vessels with rudimentary lumen formation and pleomorphic tumour cells.

**Immunoprofile**
Immunohistochemical confirmation of the diagnosis of angiosarcoma can be accomplished using antibodies directed against factor VIII, CD31 and CD34. CD31 seems to be the more sensitive and more specific antigen for endothelial differentiation. Some angiosarcomas produce cytokertatin.

**Prognosis and predictive factors**
Prognosis of renal angiosarcoma is poor with rapid development of haematogenous metastasis. The mean survival of the 19 documented cases is 7.7 months.

Malignant fibrous histiocytoma

**ICD-O code** 8830/3

Less than 50 renal MFH are documented in the literature [1269,2581]. Most of them have pararenal and retroperitoneal extension and are considered to arise from the renal capsule. They are large fleshy tumours with haemorrhage and necrosis. They can extend into the renal and caval veins.

Diagnosis of MFH relies on morphologic criteria [1845]: pleomorphic cells (spindle, round histiocyte-like and multinucleated giant tumour cells) arranged haphazardly in sheets or in short fascicles in a storiform pattern (storiform-pleomorphic type). Myxoid and inflammatory MFH variants may occur in the kidney. The two main differential diagnoses are leiomyosarcoma, the most frequent renal (or capsular) sarcoma and sarcomatoid carcinoma, which are much more frequent than MFH. Epithelioid/pleomorphic angiomyolipoma and secondary intra-renal extension of a perirenal dedifferentiated liposarcoma may also be considered. This differential diagnosis relies on immunohistochemistry and extensive sampling of the tumour to exclude a tiny carcinomatous component.

Fig. 1.93 Malignant fibrous histiocytoma.
**Angiomyolipoma**

**Definition**
Angiomyolipoma (AML) is a benign mesenchymal tumour composed of a variable proportion of adipose tissue, spindle and epithelioid smooth muscle cells, and abnormal thick-walled blood vessels.

**ICD-O code** 8860/0

**Epidemiology**

**Age and sex distribution**
In surgical series which are usually over-represented by non-tuberous sclerosis (TS) cases there is a 4:1 female predominance (1299,1825,2503,2628), but there is no apparent sex predilection in TS patients with AML detected by imaging techniques (487). The mean age at diagnosis in surgical series is between 45 and 55 for patients without TS and between 25 and 35 for those with TS (1299,1825,2503,2628). It is possible that puberty influences the development of AML (487).

**Incidence**
AMLs account for approximately 1% of surgically removed renal tumours. It has been considered an uncommon neoplasm, but its frequency is increasing because it is detected in ultrasonographic examinations performed to evaluate other conditions (816). It can occur sporadically or in patients with TS, an inherited autosomal dominant syndrome (910). Most surgical series report four times as many sporadic AMLs as AMLs associated with TS (1299,1825,2503,2628).

**Etiology**
AML is believed to belong to a family of lesions characterized by proliferation of perivascular epithelioid cells (PEC) (268,269,785,917,1171,2707,2920). Recent molecular studies have demonstrated its clonality (933,2008), and immunohistochemical and ultrastructural studies support the idea of histogenesis from a single cell type (269,1103,2511,2570,2920). The etiology and pathogenesis of the neoplasm are unknown. The different frequency of AML in females and males in the surgical series, the onset of AML after puberty and the frequent progesterone receptor immunoreactivity in AML (1077) suggest a hormonal influence.

**Localization**
AMLs may arise in the cortex or medulla of the kidney. Extrarenal growth in the retroperitoneal space with or without renal attachment can occur. Lesions may be multifocal (2570). Multifocal AML in the kidney indicates a presumptive diagnosis of TS.

**Clinical features**

**Signs and symptoms**
Clinical features differ, depending on the presence or absence of TS. In TS, AMLs are usually asymptomatic and discovered by radiographic screening techniques. Patients without TS present with flank pain, haematuria, palpable mass, or a combination of these signs and symptoms. Retroperitoneal haemorrhage may occur (2503). Simultaneous occurrence of AML with renal cell carcinoma (RCC) and oncocytoma in the same kidney has also been reported (1224). Another interesting aspect of AML is the association with lymphangioleiomyomatosis (LAM), a progressive disease which usually affects the lungs of young women and which is also related to TS. Histopathological and genetic studies have demonstrated that AML and LAM share numerous features (268,2909).

**Imaging**
Computerized tomography (CT) and ultrasonography permit the preoperative diagnosis of AML in almost all cases. High fat content, which is present in most AMLs, is responsible for a distinctive pattern on a CT scan. Tumours composed predominantly of smooth muscle cells or with an admixture of all three compo-

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Fig. 1.94 Angiomyolipoma of the kidney. CT scan of angiomyolipoma characterized by high fat content.

Fig. 1.95 A Angiomyolipoma. Large tumour with hemorrhagic component. B A large tumour with high lipid content, bulging into the perirenal fat is seen. Match with CT. C Multiple angiomyolipomas of the kidney.
nents or with prominent cystic change may be difficult to distinguish from an epithelial neoplasm preoperatively (2388). In some of these cases the diagnosis is possible by fine-needle aspiration, supplemented if necessary by immunohistochemistry (275).

Macroscopy
AMLs usually are well demarcated from the adjacent kidney, but not encapsulated. The colour varies from yellow to pinkish, depending on the relative proportions of the various tissue components. Tumours composed of all three components may mimic a clear cell RCC whereas a smooth muscle predominant AML may mimic a leiomyoma. Although AMLs may grow to great size, they bulge into rather than infiltrate the perirenal fat. Most AMLs are solitary, but multiple tumours may be present; in such situations, a large dominant tumour associated with smaller lesions is typical.

Tumour spread and staging
Infrequently, AML extends into the intrarenal venous system, the renal vein or the vena cava. Vascular invasion and multifocality have occasionally been misinterpreted as evidence of malignancy and metastasis. Regional lymph node involvement can occur; it is considered to represent a multifocal growth pattern rather than metastasis (18,2570). Only three cases of sarcoma developing in sporadic AML have been reported; two patients had pulmonary metastases and one had hepatic metastases (466,757,1636).

Histopathology
Most AMLs are composed of a variable mixture of mature fat, thick-walled poorly organized blood vessels and smooth muscle (classic triphasic histology). The border between AML and the kidney is typically sharp, although renal tubules may be entrapped at the periphery of some tumours. The smooth muscle cells appear to emanate from blood vessel walls in a radial fashion, and expansile growth thereafter may be fascicular. The smooth muscle cells are most frequently spindle cells but may appear as rounded epithelioid cells. Rarely, striking degrees of nuclear atypia (occasionally with mitotic activity and multinucleation) may be seen in these cells, raising the possibility of malignancy. Some AMLs that are often located subcapsularly and composed almost entirely of smooth muscle cells ("capsulomas") resemble leiomyomas. Cells associated with thin-walled, branching vessels with a pattern similar to lymphangioleiomyoma is another variation of the smooth muscle component. The lipomatous component consists typically of mature adipose tissue but may contain vacuolated adipocytes suggesting lipoblasts, thus mimicking a liposarcoma when there is extensive adipocytic differentiation. The blood vessels are thick-walled and lack the normal elastic content of arteries. AMLs with a prominent vascular component may mimic a vascular malformation. Prominent cystic change may very rarely be present in AML.

Immunoprotein
AMLs are characterized by a coexpression of melanocytic markers (HMB45, HMB50, CD63, tyrosinase, Mart1/Melan A and microphthalmia transcription factor) and smooth muscle markers (smooth muscle actin, muscle-specific actin and calponin); CD68, neuron-specific enolase, S-100 protein, estrogen and progesterone receptors, and desmin may also be positive, whereas epithelial markers are always negative (125,762,1254,1258,1419,2037,2922). Coexpression of

Fig. 1.96 Angiomyolipoma. A Microscopic angiomyolipoma composed of smooth muscle with a minority of fat cells, arising in the renal interstitium. B Rarely, angiomyolipoma may closely resemble renal oncocytoma.
melanocytic and smooth muscle markers in myoid-appearing and lipid-distended cells supports the unitary nature of AML being a neoplasm with ability for phenotypic and immunotypic modulation.

Ultrastructure
Ultrastructurally, AMLs show spindle cells with features of smooth muscle cells. Some spindle cells contain lipid droplets indicating transition forms between smooth muscle cells and adipocytes [1103]. Ultrastructural evidence of melanogenesis is reported, and intracytoplasmic membrane-bound dense bodies, crystals and granules (rhomboid and spherical) have been linked to renin and premelanosomes without conclusive or consistent evidence [1825, 2796, 2913].

Precursor lesions
Small nodules with some features of AML are often present in the kidney bearing AMLs, suggesting that these lesions may be the source of AMLs. The smallest nodules are often composed predominantly of epithelioid smooth muscle cells, and the proportion of spindle cells and adipocytes increase as the lesions become larger [459]. Intraglomerular lesions with features overlapping those of AML have been reported in patients with and without TS [1315, 1632, 1865].

Somatic genetics
Two genes are known to cause TS. The TSC1 gene is located on chromosome 9q34, consists of 23 exons and encodes hamartin, a 130 kDa protein [2704]. The TSC2 gene is located on chromosome 16p13, consists of 41 exons and encodes tuberin, a 180 kDa GTPase-activating protein for RAP1 and RAB5 [2604]. Tuberin and hamartin interact with each other, forming a cytoplasmic complex [1878, 2088]. AML frequently shows loss of heterozygosity (LOH) of variable portions of TSC2 gene locus in both sporadic and TS-associated tumours [370, 1078]. TSC1 gene is involved occasionally in LOH.

Prognosis and predictive factors
The classic AMLs are benign. A very small minority are associated with complications and morbidity and mortality [1936]. Haemorrhage into the retroperitoneum, usually in tumours greater than 4.0 cm or in pregnant patients, may be life threatening. Renal cysts and multiple AMLs in TS patients can lead to renal failure [2321].

Fig. 1.98 Angiomyolipoma of the kidney. LOH of TSC2 gene locus in both sporadic and tuberous sclerosis-associated tumours.

Fig. 1.99 Intraglomerular lesion associated with angiomyolipoma of the kidney. Focal positive immunoreactivity to actin in a glomerulus containing a group of smooth muscle epithelioid cells. SMA expression.
Epithelioid angiomyolipoma

**Definition**
Epithelioid angiomyolipoma (AML) is a potentially malignant mesenchymal neoplasm characterized by proliferation of predominantly epithelioid cells and is closely related to the triphasic (classic) AML.

**Epidemiology**
More than half of patients with epithelioid AML have a history of tuberous sclerosis (TS), which is a significantly higher association than classic AML has with TS [50,2036,1346]. Both sexes are equally affected similar to classic AML occurring in TS patients. The mean age of diagnosis is 38 years [649,50,463,466,593,1606,1634].

**Clinical features**
Patients are frequently symptomatic, presenting with pain; some patients are discovered during TS follow-up. Imaging studies closely mimic renal cell carcinoma because of the paucity of adipose tissue [1289,463,224].

**Macroscopy**
Tumours are usually large, with infiltrative growth and a grey-tan, white, brown or haemorrhagic appearance. Necrosis may be present. Extrarenal extension or involvement of the renal vein/vena cava may occur.

**Histopathology**
There is a proliferation of epithelioid cells with abundant granular cytoplasm arranged in sheets, often with perivascular cuffing of epithelioid cells. Many of the reported cases were initially misdiagnosed as a high grade carcinoma. Tumour cells are round to polygonal with enlarged vesicular nuclei often with prominent nucleoli.

**Fig. 1.100** Epithelioid angiomyolipoma. A Epithelioid angiomyolipoma is typically composed of a mixture of polygonal and spindle cells of variable size. Inflammatory cells often are mingled with the neoplastic cells. B Focally ganglion like and multinucleated cells are present.

**Fig. 1.101** Epithelioid angiomyolipoma. A Marked nuclear atypia and mitotic figures may be present. B Immunohistochemical reaction with HMB-45 shows numerous positive cells.

M.B. Amin
Multinucleated and enlarged ganglion-like cells may be present. A population of short spindle cells is present in many tumours. Tumours may display nuclear anaplasia, mitotic activity, vascular invasion, necrosis and infiltration of perinephric fat. Haemorrhage often is prominent. A few cases have focal classic AML areas (649,466). Variations in histology include variable admixture of clear cells, although occasionally they may predominate (2184,560).

**Immunoprofile**
Epithelioid AML expresses melanocytic markers (HMB-45, HMB-50, Mart-1/Melan-A and microphthalmia transcription factor) with variable expression of smooth muscle markers (smooth muscle actin, muscle-specific actin) (125,1419, 2922,2511).

**Genetics**
Allelic loss of chromosomal arm 16p (TS2 containing region) is noted in classic, epithelioid and sarcomatoid areas indicating clonality and relationship (2497). TP53 mutation is detected in epithelioid but not triphasic AML, suggesting a role in malignant transformation (1289).

**Prognostic and predictive factors**
Approximately one-third of epithelioid AML have been reported to have metastasis to lymph nodes, liver, lungs or spine (1565,1636,757,2863). Among adverse pathologic parameters, none correlate with outcome; however, tumours with necrosis, mitotic activity, nuclear anaplasia and extrarenal spread should raise significant concern for malignant outcome (463,466,2036,757,2863).
Leiomyoma

Definition
Leiomyoma is a benign smooth muscle neoplasm.

ICD-O code 8890/0

Epidemiology and etiology
A leiomyoma may arise from the renal capsule (most common), muscularis of the renal pelvis, or from cortical vascular smooth muscle (273,624,1762,2502, 2585). Most are encountered in adults as incidental small mm-sized capsular tumours at autopsy. They may on occasion be large (largest case reported 37 kg), resulting in surgery for a presumed carcinoma (273,624,2502).

Macroscopy
Macroscopically, leiomyomas are firm well-demarcated solid lesions. Large examples have a trabeculated cut surface. Calcification and cystic change have been described, but necrosis should not be present.

Histopathology
Histologically, they are composed of spindled cells, usually arranged in intersecting fascicles with little nuclear pleomorphism and no mitotic activity. They have a smooth muscle immunophenotype, demonstrating a positive reaction on actin and desmin stains (273,508, 2585). Some focally express HMB-45, suggesting a relationship to angiomyolipoma and other tumours of the perivascular epithelioid cell family of tumours (273).
Haemangioma

Definition
Haemangioma is a benign vascular tumour that occasionally arises in the kidney.

ICD-O code 9120/0

Epidemiology
These tumours most commonly affect young to middle aged adults; however, the youngest reported patient was a newborn (2916). There is no sex predilection. A number of these tumours are asymptomatic and are discovered incidentally at autopsy (1205).

Clinical features
Symptomatic patients present with recurrent episodes of hematuria. Colicky pain may also be noted, caused by the passage of blood clots. In addition to sporadic tumours, haemangiomas may be part of a syndrome such as Slurge-Weber syndrome, Klippel-Trenaunay syndrome and systemic angiomatosis.

Macroscopy
Haemangiomas are generally unilateral and single, but may rarely be multifocal or bilateral (2573,2916). The largest haemangioma reported to date was 18 cm in greatest diameter (2875). Renal pyramids and renal pelvis are the most common sites of involvement, rarely these tumours may be found in the renal cortex or the renal capsule (2779). On cut section they are unencapsulated, have a spongy red appearance, or may be apparent as a small red streak.

Histopathology
Both capillary and cavernous haemangiomas have been reported, the latter being more common. A case of intravascular capillary haemangioma, arising in a renal vein, and presenting as a renal mass has also been reported (1145). They exhibit the typical histologic features of haemangiomas, i.e, irregular blood-filled vascular spaces lined by a single layer of endothelial cells. They may show an infiltrative growth pattern, but lack the mitosis and nuclear pleomorphism seen in angiosarcomas.

Lymphangioma

Definition
Lymphangioma is a rare benign renal tumour that may arise from the renal capsule, develop within the cortex, or most often, present as a peripelvic or renal sinus mass.

ICD-O code 9170/0

Epidemiology and etiology
These lesions are more common in adults. Children account for 1/3 of cases. Some cases may develop secondary to inflammatory lower urinary tract diseases, or represent a developmental abnormality in lymphatic formation. A bilateral presentation in children is referred to as lymphangiomatosis (1462). Some cases appear neoplastic with karyotype abnormalities such as monosomy X, trisomy 7q, and defects in the von Hippel Lindau gene (358,578). They are usually treated by nephrectomy because preoperative investigations cannot distinguish them from a malignant neoplasm.

Macroscopy
Lymphangiomas are encapsulated, diffusely cystic lesions ranging from small well-delineated tumours to large (19 cm) lesions that replace the entire renal parenchyma (89,1867,2921).

Histopathology
The cysts communicate, contain clear fluid, and are composed of fibrous septae lined by flattened endothelium that is factor VIII and Ulex europaeus agglutinin positive but cytokeratin negative. The fibrous septa may contain small bland entrapped native tubules and lymphoid cells. Smooth muscle may be present as in lymphangiomas elsewhere.
Definition
Juxtaglomerular cell tumour is a benign renin-secreting tumour.

ICD-O code 8361/0

Epidemiology
Since the first description in 1967 (2213) over 60 JGCTs have been reported (1638). JGCT usually occurs in younger individuals, averaging 27 years, and is twice as common in women. There is no reported recurrence or metastasis despite an interval of up to 17 years between the onset of hypertension and nephrectomy (1790) and a follow-up of up to 17 years after surgery (978).

Localization
JGCT is unilateral, cortical and arises equally in both kidneys and in either pole.

Clinical features
The diagnosis of JGCT is usually suspected in patients with severe poorly controlled hypertension and marked

Fig. 1.104 Juxtaglomerular cell tumour.

Fig. 1.105 Juxtaglomerular cell tumour. A Solid growth pattern of polygonal cells. B Higher magnification demonstrates pale halos about the nuclei.

Fig. 1.106 Juxtaglomerular cell tumour. A Occasionally, the tumour may contain channels lined by epithelium. B Rarely, extensively papillary architecture may be seen.
hypokalemia, although one patient presented with normal blood pressure (1044). Investigation discloses high plasma renin activity, elevated secondary hyperaldosteronism and a renal mass. Hypertension and hypokalemia resolve after surgery.

**Macroscopy and histopathology**

JGCT is solid, well-circumscribed and yellow-tan. The tumour is usually smaller than 3 cm in diameter but cases ranging from 2 mm (1097) to 9 cm (1413) have been reported. JGCT is histologically made of sheets of polygonal or spindled tumour cells with central round regular nuclei, distinct cell borders and abundant granular eosinophilic cytoplasm staining for the Bowie stain, PAS and toluidine blue. Typically, tumours present with a complex vascular haemangiopericytic pattern. Mast cells and thick-walled hyalinized blood vessels are common and, in about one-half of reported cases, prominent tubular elements either neoplastic or entrapped are also present. Rarely, JGCT may be largely papillary (2602). Tumour cells are immunoreactive for renin, actin, vimentin and CD34 (1638). Ultrastructural features include abundant rough endoplasmic reticulum, a well developed Golgi apparatus and numerous peripherally located sharply angulated rhomboid renin protogranules. A variable number of round electron-dense mature renin-like granules are also found.
Renomedullary interstitial cell tumour

ICD-O code 8966/0

Renomedullary interstitial cell tumours are common autopsy findings in adults (2161,2163,2783). They are present in nearly 50% of men and women. About half the patients who have one renomedullary interstitial cell tumour have more than one. They are asymptomatic and while renomedullary interstitial cells play a role in regulation of blood pressure, renomedullary interstitial cell tumours have no clear influence on blood pressure.

Almost all renomedullary interstitial cell tumours are 1-5 mm in diameter and appear as white or pale grey nodules within a renal medullary pyramid. Rarely, they are larger (1604) and can form polypoid masses protruding into the renal pelvic cavity (896).

Microscopically, renomedullary interstitial cell tumours are seen to contain only small amounts of collagen. The renomedullary interstitial cells are small stellate or polygonal cells in a background of loose faintly basophilic stroma reminiscent of renal medullary stroma. At the periphery, renal medullary tubules often are entrapped in the matrix. Interlacing bundles of delicate fibers usually are present. Some renomedullary interstitial cell tumours contain deposits of amyloid. In these, the delicacy of the stroma is lost and irregular eosinophilic deposits of amyloid are present within the nodule.

Fig. 1.110 Renomedullary interstitial cell tumour forms a white nodule in a medullary pyramid.

Fig. 1.111 Renomedullary interstitial cell tumour. A Well circumscribed tumour composed of spindle cells in a basophilic matrix. B Note deposits of amyloid. C This example is sparsely cellular and composed of interlacing bands of nondescript spindle cells.
Intrarenal schwannoma

**ICD-O code** 9560/0

Schwannoma is a common, benign tumour of peripheral and auditory nerves (723). Its occurrence in the kidney is very rare, with only eighteen reported cases (73,2424). Distribution of the 18 renal schwannomas was as follows: parenchyma, 33%; hilum 28%; pelvis 28%; capsule 11% (73,1585, 2424).

Patients have nonspecific symptoms and signs. Malaise, weight loss, fever, and abdominal or flank pain are common findings. A palpable abdominal mass is frequently present. Hematuria may also be present (73,2424,2460). Tumours are well circumscribed, sometimes lobulated, rounded masses, 4 to 16cm (mean 9.7cm) in diameter and vary in colour from tan to yellow (1167,2653).

Microscopically, renal schwannoma is composed of spindle cells often arranged in a palisading fashion (Antoni A pattern) and less cellular loosely textured tumour areas (Antoni B) (2424). Some tumours display the histologic features of cellular schwannomas, with hypercellular areas composed exclusively or predominantly of Antoni A tissue, and devoid of Verocay bodies (2839).

Solitary fibrous tumour

**ICD-O code** 8815/0

The lesion may be clinically confused with renal cell carcinoma or sarcoma because of its large size by physical examination and radiographic studies as well as the frequent presence of painless hematuria (1595,2778). The tumours are grossly well-circumscribed masses arising in the renal parenchyma. They are variable incellularity, consisting of a mixture of haphazard, storiform, or short fascicular arrangements of bland spindle cells and less cellular dense collagenous bands. A haemangiopericytoma-like growth pattern is typically seen. Immunostaining for CD34, bcl-2 and CD99 confirms the diagnosis.

Fig. 1.12 Solitary fibrous tumour. Haphazard proliferation of uniform spindle cells with strong immunoreactivity for CD34.
**Cystic nephroma**

**Definition**
Cystic nephroma is a benign cystic neoplasm composed of epithelial and stromal elements.

**ICD-O code** 8959/0

**Epidemiology**
Typically, cystic nephroma presents after age 30 and has an 8:1 female to male ratio.

**Clinical features**
Cystic nephroma presents as a mass and cannot be distinguished radiographically from other cystic neoplasms. Pleuropulmonary blastoma is a very rare paediatric tumour associated with cystic nephroma in the same patient and in other family members [1175].

**Macroscopy**
Cystic nephroma is an encapsulated well-demarcated tumour composed entirely of cysts and cyst septa. No solid areas or necrosis is present. The cysts contain serosanguinous fluid that can occasionally appear haemorrhagic. The lesion may be focal or replace the entire kidney. Rarely, a predominantly intrapelvic presentation occurs [1411].

**Histopathology**
The cysts are lined by a single layer of flattened, low cuboidal, or hobnail epithelium. The cytoplasm may be eosinophilic or clear. The fibrous septa may be paucicellular or cellular resembling ovarian stroma. The septa may contain clusters of mature tubules.

![Figure 1.113](image1) Cystic nephroma. A The tumour consists of small and large cysts. B The tumour is sharply demarcated from an otherwise normal kidney.

![Figure 1.114](image2) Cystic nephroma. A Cystic nephroma composed entirely of cysts and septae. B Cellular details of single cell layer composed of hobnail epithelium.
**Mixed epithelial and stromal tumour**

**Definition**
Mixed epithelial and stromal tumour is a complex renal neoplasm composed of a mixture of stromal and epithelial elements.

**Synonyms**
Some authors have applied other names (cystic hamartoma of renal pelvis or adult mesoblastic nephroma) but the name "mixed epithelial and stromal tumour" best captures its nature [2035].

**Clinical features**
There is a 6:1 predominance of women over men [35]. All have been adults and the mean age is perimenopausal (46 years). Presenting symptoms include flank pain, haematuria or symptoms of urinary tract infection; 25% are incidental findings. Histories of estrogen therapy are common. Surgery has been curative in all cases.

**Macroscopy**
The tumours often arise centrally in the kidney and grow as expansile masses, frequently herniating into the renal pelvic cavity. The tumours are typically composed of multiple cysts and solid areas.

**Histopathology**
These are complex tumours composed of large cysts, microcysts, and tubules. The largest cysts are lined by columnar and cuboidal epithelium, which sometimes forms small papillary tufts. Urothelium, which may be hyperplastic, may also line some portion of the cysts. The microcysts and tubules are lined by flattened, cuboidal, or columnar cells. Their cytoplasm ranges from clear to pale, eosinophilic, or vacuolated. Epithelium with müllerian characteristics has also been described [205]. The architecture of the microcysts is varied and ranges from simple microcysts with abundant stroma between them, to densely packed clusters of microcysts, to complex branching channels which may be dilated. These varied elements often are present intermingled in the same area of the tumour. The stroma consists of a variably cellular population of spindle cells with plump nuclei and abundant cytoplasm. Areas of myxoid stroma and fascicles of smooth muscle cells may be prominent. Densely collagenous stroma is common and fat is occasionally present. Mitotic figures and atypical nuclei have not been reported.
Immunoprofile

Immunohistochemistry shows that the spindle cells, which look like smooth muscle have strong reactions with antibodies to actins and to desmin. The nuclei of the spindle cells also frequently react with antibodies to estrogen and progesterone receptors (35). The epithelial elements react with antibodies to a variety of cytokeratins and often vimentin. They occasionally react with antibody to estrogen receptor.

Genetics

Little is known of the genetics of these tumours except that they lack the translocation characteristic of cellular congenital mesoblastic nephroma (2073).

Fig. 1.118 Mixed epithelial and stromal tumour. A Complex branching tubules in a spindle cell stroma with smooth muscle differentiation. B Cysts and small tubular structures resembling nephrogenic adenoma.
Synovial sarcoma of the kidney

**Definition**
Synovial sarcoma (SS) of the kidney is a spindle cell neoplasm that infrequently displays epithelial differentiation and is characterized by a specific translocation, t(X;18)(p11.2;q11).

**ICD-O code** 9040/3

**Synonyms and historical annotation**
A subset of previously described embryonal sarcoma of the kidney is now recognized to be primary renal SS [112].

**Epidemiology**

**Age and sex distribution**
Renal synovial sarcoma occurs in an age range 12-59 years, with a mean of 35 years and shows a slight male predilection (1.6:1).

**Localization**
Tumour equally involves either kidney, but no bilateral tumours were identified.

**Clinical features**

**Symptoms and signs**
Flank or abdominal pain with or without abdominal distension is the presenting symptom in more than half of cases.

**Macroscopy**
Most of the tumours are solid, but multiple areas of haemorrhage, necrosis and cyst formation can be observed on gross examination.

**Histopathology**
Tumours are typically mitotically active, with monomorphic plump spindle cells and indistinct cell borders growing in short, intersecting fascicles or in solid sheets. Cysts are lined by mitotically inactive polygonal eosinophilic cells with apically located nuclei (“hobnailed epithelium”), and appear to be entrapped native renal tubules, which may be extensively dilated. Areas of solid aggregation or fascicles of the tumour cells alternating with hypocellular myxoid tissues, together with areas displaying a prominent haemangiopericytoma-like pattern, may be found. Rhabdoid cells in the tumour have been recently described [1253].

**Immunoprofile**
The tumour cells are consistently immunoreactive with vimentin and BCL2, frequently reactive for CD99 but desmin and muscle specific actin are negative. The tumour cells are often negative or only focally positive for cytokeratins (AE1/AE3, or CAM 5.2) and epithelial membrane antigen, but the epithelial lin-

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**Fig. 1.119** Synovial sarcoma of the kidney.

**Fig. 1.120** Renal synovial sarcoma. **A** Note prominent cystic change. **B** The cysts are lined by hobnail epithelium with abundant eosinophilic cytoplasm representing entrapped dilated tubules. **C** Higher magnification shows monomorphic small spindle cells.
ing cells of the cysts are consistently highlighted by these markers [112,1316].

**Genetics**

Synovial sarcoma is cytogenetically characterized by the translocation t(X;18) (p11.2;q11.2) generating a fusion between the SYT gene on chromosome 18 and one member of the SSX family gene (SSX1;SSX2;SSX4) on chromosome X.

Molecularly confirmed primary renal synovial sarcomas have demonstrated the characteristic SYT-SSX gene fusion [112, 1316,1379]. In contrast to soft tissue synovial sarcoma where the SYT-SSX1 gene fusion is more common than the alternative SYT-SSX2 form [1422], the majority of renal synovial sarcomas have so far demonstrated the SYT-SSX2 gene fusion [112,1316,1379]. In soft tissue synovial sarcomas, the SYT-SSX2 form of the gene fusion is strongly correlated with monophasic histology [1422]; this tendency is also consistent with the predominance of monophasic spindled morphology of these tumours in the kidney and the rarity of biphasic histology.

**Prognosis and predictive factors**

Prognostic data are limited, some have responded to chemotherapy, however recurrence is common.
Renal carcinoid tumour

Definition
A well differentiated neuroendocrine neoplasm arising within the kidney.

ICD-O code
8240/3

Epidemiology
Primary renal carcinoid is very rare, only about 50 cases having been reported and there appears to be an association with horseshoe kidney [202,1180,1662, 1690,2463,2878]. There is no sex predilection. Presentation is most common in the fourth to seventh decades, including a range from 13-79 years (mean, 49 years; median, 51 years).

Clinical features
The most common mode of presentation is abdominal pain, mass, or haematuria. Carcinoid syndrome symptoms are uncommon (<10%) [1006,1819, 2150,2174]. Computed tomography usually reveals a circumscribed and solid mass with an occasional cystic component or calcification. Somatostatin receptor scintigraphy (pentetreotide scan) is of adjunct value in staging and surveillance for the development of recurrent or metastatic disease [1662].

Macroscopy
Renal carcinoid is a solitary tumour with a well circumscribed, lobulated and bulging appearance. The tumour is yellow-tan, beige-white or red-brown, and has a soft to moderately firm consistency. The appearance is homogeneous or may depict focal haemorrhage, calcification and cystic changes, whereas necrosis is uncommon [203,903,1764,2150].

Tumour spread and staging
Capsular invasion and/or renal vein involvement (pT3) has been reported.

Histopathology
Renal carcinoid displays the typical histologic features of carcinoids in other organs of the body.

Immunoprofile
The immunohistochemical profile is similar to that of carcinoid tumours elsewhere. [202,203,759,903,1764,2150, 2688]. Immunoreactivity for prostatic acid phosphatase (PAP) has been documented in at least five tumours [202,203, 677,903,2560].

Somatic genetics
Only a few tumours have been studied by genetic methods [677,2688].

Prognosis
The clinical outcome is difficult to predict and a significant proportion of patients with metastatic disease have a protracted clinical course.
Neuroendocrine carcinoma of the kidney

**Definition**
A poorly-differentiated epithelial neoplasm showing neuroendocrine differentiation.

**ICD-O code** 8246/3

**Epidemiology**
Accounts for much less than 1% of all epithelial renal malignancies, neuroendocrine carcinoma of the kidney occurs in adults (average age: 60 years) with no sex predilection.

**Clinical features**
Abdominal pain and gross haematuria are the most frequent clinical symptoms [727,971,2601].

**Macroscopy**
Most neuroendocrine carcinomas of the kidney are located close to the renal pelvis, often surrounding the pelvicaliceal cavities. The tumour presents as a soft, whitish, gritty and necrotic renal mass, often extending into renal sinus adipose tissue. Tumours range in size from 2.5 to 23 cm (median: 8 cm) [368, 727,971,1326,1658,1735,2601].

**Histopathology**
Morphologically, the tumour is composed of sheets, nests and trabecula of apparently poorly-differentiated small, round to fusiform cells separated by sparse intervening stroma. These cells show characteristic hyperchromatic nuclei with stippled chromatin and inconspicuous nucleoli. Their cytoplasm is hardly visible on HE sections. Mitoses are numerous, vascular tumour emboli common, and tumour necrosis often extensive and accompanied with perivascular DNA deposition (Azzopardi phenomenon). A concomitant urothelial carcinoma is common [727,971,1326,1658].

**Immunoprofile**
Immunohistochemically, tumour cells show dot-like cytoplasmic staining with cytokeratins and are variably positive for neuroendocrine markers including chromogranin A, synaptophysin, CD56 (N-Cam), and neuron specific enolase [727,971,1658,1735].

**Prognosis and predictive factors**
The prognosis is poor and stage dependent. Most patients present with large and locally aggressive tumours, often extending into perirenal adipose tissue at diagnosis [368,727,971,1658]. Regional lymph nodes and distant metastases are common [368,971,1658,1735,2601]. At least, 75% of patients die of their disease within one year [727,971,1326,1658,1735,2601] regardless of treatment.

**Fig. 1.126** Small cell carcinoma of the kidney. A Large, centrally located, necrotic tumour with renal pelvis invasion. From L. Guillou et al. (971) B,C Tumour cells show scant cytoplasm and granular chromatin with inconspicuous nucleoli. Note nuclear molding and numerous mitoses.
Primitive neuroectodermal tumour (Ewing sarcoma)

Definition
A malignant tumour composed of small uniform round cells, characterized by a translocation resulting in a fusion transcript of the EWS gene and ETS-related family of oncogenes.

ICD-O codes
Ewing sarcoma 9260/3
Peripheral neuroectodermal tumour 9364/3

Epidemiology
This neoplasm is rare [2009,2124]. A review of 35 cases of renal PNET-EWS revealed an age range from 4-69 years which is somewhat wider than that recorded for this tumour in the bone and soft tissues. The mean age was 27 years with a median age of 21 years. There was a predilection for males (21 males, 14 females).

Clinical features
Signs and symptoms
Abdominal pain of recent (weeks) or sudden onset, flank pain and gross haematuria were the most common presenting symptoms. Fever, weight loss and bone pain were other less frequent manifestations. A palpable abdominal or flank mass was detected in less than 25% of cases. Pulmonary, hepatic and bony metastases were noted at presentation in 10% of patients [385].

Imaging
A sizable, inhomogeneous mass often replacing almost the entire kidney was the common computed tomographic appearance [630]. Areas of high and low intensity reflected the common presence of haemorrhage and necrosis in resected specimen.

Macroscopy
A mass measuring in excess of 10 cm in diameter with replacement of the kidney and weighing 1 kg or more in some cases served to characterize these neoplasms as a group [1225]. Cross-sect-
tional features included a greyish-tan to white lobulated surface with interspersed areas of haemorrhage and necrosis. A capsule or pseudocapsule was described in a minority of tumours.

Histopathology
The tumour in the kidney is no different than the more common counterpart in soft tissues. The cells are relatively monotonous polygonal cells whose appearance is dominated by a hyperchromic rounded nucleus. A finely dispersed chromatin and a micronucleolus in some cases are the nuclear characteristics. Interspersed smaller "dark" cells

Fig. 1.127 A PNET of the kidney. B Renal PNET. Note sheet-like growth pattern and rosettes.
representing tumour cells undergoing pyknosis are prominent in some cases. Mitotic figures may be numerous. Though the nuclear to cytoplasmic ratio is high, a rim of clear cytoplasm and discrete cell membranes are often apparent in well-fixed tumours without extensive degenerative changes. The presence of clear cytoplasm is often associated with abundant glycogen as demonstrated by diastase sensitive PAS-positivity.

**Immunoprofile**

The basic immunophenotype of PNET-EWS, regardless of the primary site, is the expression of vimentin and the surface antigen of the MIC2 gene, CD99 (O13) or HBA-71. Approximately 20% of cases also express pan-cytokeratin. The staining pattern for vimentin and cytokeratin may be perinuclear or Golgi zone punctate reactivity.

**Somatic genetics**

Virtually all of the recently reported PNET-EWSs have had the t(11;22)(q24;q12) translocation with the fusion transcript between the EWS gene (22q12) and the ETS-related oncogene, FLI1 (11q24) (1627,2124). Variant translocations with EWS are those with other ETS-related oncogenes: (21q22), (7p22), (17q12) and (2q33).

**Prognosis**

Pathologic stage is the major determinant in the prognosis of PNET-EWS regardless of the primary site. Aggressive multidrug chemotherapy has resulted in an improvement in the clinical outcome (525).

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**Neuroblastoma**

**ICD-O code** 9500/3

Neuroblastomas arising as a true intrarenal mass are extremely rare; only six cases were identified in the National Wilms Tumour Study Pathology Centre in 1993 (2225). Pure intrarenal lesions hypothetically arise from either adrenal rests or intrarenal sympathetic tissue (2385). Far more frequently, adrenal neuroblastomas invade the adjacent kidney; this occurs in approximately five per cent of cases (2375). Because most neuroblastomas arise from the adrenal, those affecting the kidney predominate in the superior pole. Extensive renal sinus invasion may simulate a pelvic tumour. Preoperative determination of urine catecholamine excretion is helpful in diagnosis of neuroblastoma but may not exclude nephroblastomas with neural elements (2273). The presence of primitive neural tissue defines neuroblastomas, which contain Homer Wright rosettes, neurofibrillar stroma, and embryonal cells with round nuclei containing granular, “salt and pepper” chromatin. Important positive indicators of neuronal differentiation include neuron-specific enolase, synaptophysin, S100 protein, and chromogranin.
**Paraganglioma / Phaeochromocytoma**

**ICD-O codes**
- Paraganglioma 8680/1
- Pheochromocytoma 8700/0

A very small number of tumours have been described in the kidney [595, 1426]. Most tumours are small. The cut surface is grey, often well vascularized. The colour of the parenchyma often rapidly turns brown when exposed to air. This is due to oxidation of chromaffin substances, including catecholamines. The architecture is characterized by cell clusters (‘Zellballen’) surrounded by a network of fine collagenous septa, containing blood vessels and sustentacular cells. The immunoreactions for synaptophysin, chromogranin A, and CD56 are consistently strong in virtually all tumour cells. Protein S-100 highlights tumour cells and sustentacular cells.

**Lymphomas**

**Definition**
Primary renal lymphoma is a lymphoma without evidence of systemic involvement.

**Epidemiology**
Less than 100 cases of primary renal lymphomas, both Hodgkin disease and non-Hodgkin lymphoma, have been described. However, post-transplant lymphoproliferative disorders are the most frequently encountered disorder today. In the non-transplant patients, primary lymphomas may present as a mass lesion and regarded clinically as a renal epithelial neoplasm and treated by nephrectomy. The diagnosis requires renal and bone marrow biopsy and thoraco-abdominal CT [2477]. Dissemination following the diagnosis of PRL is common. Secondary renal lymphomas (SRL) affect the kidney as the second most common site for metastasis [2284]. It is 30x more common than PRL [374, 537]. Most present (48%) in advanced stage lymphoma [1267].

**Etiology**
PRL arising in transplanted kidneys are usually EBV-associated monomorphic or polymorphic B-cell lymphoproliferations of donor origin and related to iatrogenic immunosuppression [439, 839, 1695, 2833].

**Clinical features**
Common symptoms are flank or abdominal pain, haematuria, fever, weight loss, hypertension, renal insufficiency, or acute renal failure [448, 537, 626, 1354, 2097, 2382]. Complications are renal failure [750] and paraneoplastic hypercalcemia [2676].

**Macroscopy**
Nephrectomy specimens in primary or secondary lymphoma show single or multifocal nodules (eventually associated with hydronephrosis) or diffuse renal enlargement. In secondary lymphoma, bilateral involvement is frequent (10% to 30%) [13, 1881, 2097, 2408, 2647, 2696]. The cut surface is usually homogeneous, firm and pale, but necrosis, haemorrhage, cystic changes, calcifications and tumoral thrombus formation in the renal vein may occur [2677, 2760]. Intravascular large B-cell lymphoma almost always affects the kidneys but may cause no macroscopic change [2819].

**Histopathology**
There are three patterns of renal involvement. The most common is diffuse involvement with lymphoma cells permeating between the native nephron structures resulting in marked organ enlargement. The second pattern is formation of one or more tumour masses. The least common pattern is the intravascular form where lymphoma cells fill all vascular components. Almost every histological lymphoma subtype may be encountered. Diffuse large B-cell lymphoma, including its variants, constitutes the single most frequent type of PRL and SRL [448, 750, 755, 2097, 2647].

**Prognosis and predictive factors**
Secondary renal lymphoma usually indicates stage IV disease with dismal prognosis [327, 622, 1267, 2097]. In PRL, dissemination to extrarenal sites is common and confers a bad prognosis as well [622]. Modern radiochemotherapy has improved survival and renal functional compromise [2097, 2696].

Fig. 1.129 Lymphoma.
Plasmacytoma (PC) of the kidney most often occurs as a manifestation of disseminated multiple myeloma. The kidney, however, may rarely be the site of origin of a solitary (primary) extraosseous PC (1266,2933). PC of the kidney is histologically indistinguishable from plasmacytoma occurring elsewhere. To qualify as a primary PC, a complete radiologic work-up must show no evidence of other lesions. The bone marrow must show no evidence of plasmacytosis and/or plasma cell monoclonality. The other myeloma associated criteria are also absent.

**Fig. 1.130** Plasmacytoma involving the kidney in a patient with disseminated multiple myeloma. A The low power photomicrograph shows a well demarked nodular lesion surrounded by unremarkable kidney parenchyma. B High magnification illustrating the plasma cell proliferation which is characterized by a mixture of both mature and immature plasma cells.
Leukaemia

Interstitial infiltration of leukaemic cells without a nodular mass is best referred to as extramedullary leukaemia in kidney. Diffuse infiltration of the kidney secondary to acute myeloid and lymphoblastic leukaemias, megakaryoblastic leukaemia, or chronic lymphocytic leukaemia has rarely been reported in the literature (989). Myeloid sarcoma (MS) is a neoplastic proliferation of myeloblasts or immature myeloid cells forming a mass in an extramedullary site. MS may occur "de novo" or simultaneously with acute myeloid leukemia, myeloproliferative disorder, or myelodysplastic syndrome (154,989). It may represent the first manifestation of leukaemia relapse in a previously treated patient. The commonest type of myeloid sarcoma occurring in the kidney is known as granulocytic sarcoma, a tumour composed of myeloblasts and promyelocytes (154).

Germ cell tumours

Primary renal choriocarcinomas have rarely been reported and are difficult to distinguish from high grade urothelial carcinomas with syncytiotrophoblasts. Most of the cases in the literature (1019, 1135) are metastases from testicular germ cell tumours (1168,1728,1804). The wide range of differentiation in nephroblastoma can resemble teratoma. Reports of teratomas of the kidney are very rare. Reported cases have involved the renal parenchyma or the renal hilus and have been indistinguishable from teratomas of the gonads. (6,138,580, 916,1986,2878).