CHAPTER 2

Tumours of the Urinary System

With approximately 260,000 new cases per year worldwide, tumours of the urinary system contribute significantly to the overall human cancer burden. Progress in the early detection and treatment of bladder cancer has improved the prognosis, with five-year survival rates of 60 - 80%.

The origin of bladder cancer is multifactorial, with tobacco smoking as the principal cause in most countries. Other etiological factors include analgesic abuse, occupational exposure and chronic Schistosoma cystitis.

Urothelial carcinomas are the most frequent and important tumour type. Improvements in early detection have made reproducible grading and staging important criteria for clinical management and prognosis.
WHO histological classification of tumours of the urinary tract

<table>
<thead>
<tr>
<th>Urothelial tumours</th>
<th>Neuroendocrine tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infiltrating urothelial carcinoma 8120/3</td>
<td>Small cell carcinoma 8041/3</td>
</tr>
<tr>
<td>with squamous differentiation</td>
<td>Carcinoid 8240/3</td>
</tr>
<tr>
<td>with glandular differentiation</td>
<td>Paragangioma 8680/1</td>
</tr>
<tr>
<td>with trophoblastic differentiation</td>
<td><strong>Malignant melanoma</strong> 8720/3</td>
</tr>
<tr>
<td>Nested</td>
<td>Nevis</td>
</tr>
<tr>
<td>Microcystic</td>
<td></td>
</tr>
<tr>
<td>Micropapillary 8131/3</td>
<td></td>
</tr>
<tr>
<td>Lymphoepithelioma-like 8082/3</td>
<td></td>
</tr>
<tr>
<td>Lymphoma-like</td>
<td></td>
</tr>
<tr>
<td>Plasmacytoid</td>
<td></td>
</tr>
<tr>
<td>Sarcomatoid 8122/3</td>
<td>Rhabdomyosarcoma 8900/3</td>
</tr>
<tr>
<td>Giant cell 8031/3</td>
<td>Leiomyosarcoma 8890/3</td>
</tr>
<tr>
<td>Undifferentiated 8020/3</td>
<td>Angiosarcoma 9120/3</td>
</tr>
<tr>
<td>Non-invasive urothelial neoplasias</td>
<td>Osteosarcoma 9180/3</td>
</tr>
<tr>
<td>Urothelial carcinoma in situ 8120/2</td>
<td>Malignant fibrous histiocytoma 8830/3</td>
</tr>
<tr>
<td>Non-invasive papillary urothelial carcinoma, high grade 8130/23</td>
<td>Leiomysoma 8890/0</td>
</tr>
<tr>
<td>Non-invasive papillary urothelial carcinoma, low grade 8130/21</td>
<td>Haemangioma 9120/0</td>
</tr>
<tr>
<td>Non-invasive papillary urothelial neoplasm of low</td>
<td>Other</td>
</tr>
<tr>
<td>malignant potential 8130/1</td>
<td></td>
</tr>
<tr>
<td>Urothelial papilloma 8120/0</td>
<td></td>
</tr>
<tr>
<td>Inverted urothelial papilloma 8121/0</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Squamous neoplasms</th>
<th>Haematopoietic and lymphoid tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma 8070/3</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Verrucous carcinoma 8051/3</td>
<td>Plasmacytoma 9731/3</td>
</tr>
<tr>
<td>Squamous cell papilloma 8052/0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Glandular neoplasms</th>
<th>Miscellaneous tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma 8140/3</td>
<td>Carcinoma of Skene, Cowper and Littre glands</td>
</tr>
<tr>
<td>Enteric</td>
<td>Metastatic tumours and tumours extending from other organs</td>
</tr>
<tr>
<td>Mucinous 8480/3</td>
<td></td>
</tr>
<tr>
<td>Signet-ring cell 8490/3</td>
<td></td>
</tr>
<tr>
<td>Clear cell 8310/3</td>
<td></td>
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<tr>
<td>Villous adenoma 8261/0</td>
<td></td>
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</tbody>
</table>

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1 Morphology code of the International Classification of Diseases for Oncology (ICD-O) (8th) and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /2 for in situ carcinomas and grade III intraepithelial neoplasia, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.
## TNM classification of carcinomas of the urinary bladder

<table>
<thead>
<tr>
<th>TNM classification</th>
<th>Stage Grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T</strong> – Primary tumour</td>
<td><strong>Stage 0a</strong> Ta N0 M0</td>
</tr>
<tr>
<td><strong>TX</strong> Primary tumour cannot be assessed</td>
<td><strong>Stage 0is</strong> Tis N0 M0</td>
</tr>
<tr>
<td><strong>T0</strong> No evidence of primary tumour</td>
<td><strong>Stage I</strong> T1 N0 M0</td>
</tr>
<tr>
<td><strong>Ta</strong> Non-invasive papillary carcinoma</td>
<td><strong>Stage II</strong> T2a, b N0 M0</td>
</tr>
<tr>
<td><strong>Tis</strong> Carcinoma in situ</td>
<td><strong>Stage III</strong> T3a, b N0 M0</td>
</tr>
<tr>
<td><strong>T1</strong> Tumour invades subepithelial connective tissue</td>
<td><strong>Stage IV</strong> T4a N0 M0</td>
</tr>
<tr>
<td><strong>T2</strong> Tumour invades muscle</td>
<td><strong>Any T</strong> N1, N2, N3 M0</td>
</tr>
<tr>
<td><strong>T2a</strong> Tumour invades superficial muscle (inner half)</td>
<td><strong>Any T</strong> Any N M1</td>
</tr>
<tr>
<td><strong>T2b</strong> Tumour invades deep muscle (outer half)</td>
<td><strong>Stage IV</strong> T4b N0 M0</td>
</tr>
<tr>
<td><strong>T3</strong> Tumour invades perivesical tissue:</td>
<td></td>
</tr>
<tr>
<td><strong>T3a</strong></td>
<td></td>
</tr>
<tr>
<td><strong>T3b</strong> Macroscopically (extravesical mass)</td>
<td></td>
</tr>
<tr>
<td><strong>T4</strong> Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall</td>
<td></td>
</tr>
<tr>
<td><strong>T4a</strong> Tumour invades prostate, uterus or vagina</td>
<td></td>
</tr>
<tr>
<td><strong>T4b</strong> Tumour invades pelvic wall or abdominal wall</td>
<td></td>
</tr>
<tr>
<td><strong>N</strong> – Regional lymph nodes</td>
<td></td>
</tr>
<tr>
<td><strong>NX</strong> Regional lymph nodes cannot be assessed</td>
<td></td>
</tr>
<tr>
<td><strong>N0</strong> No regional lymph node metastasis</td>
<td></td>
</tr>
<tr>
<td><strong>N1</strong> Metastasis in a single lymph node 2 cm or less in greatest dimension</td>
<td></td>
</tr>
<tr>
<td><strong>N2</strong> Metastasis in a single lymph node node more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, none more than 5 cm in greatest dimension</td>
<td></td>
</tr>
<tr>
<td><strong>N3</strong> Metastasis in a lymph node more than 5 cm in greatest dimension</td>
<td></td>
</tr>
</tbody>
</table>

1. (944,2662).
2. A help desk for specific questions about the TNM classification is available at http://www.uicc.org/tnm/

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## TNM classification of carcinomas of the renal pelvis and ureter

<table>
<thead>
<tr>
<th>TNM classification</th>
<th>Stage Grouping</th>
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<tr>
<td><strong>T</strong> – Primary tumour</td>
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</tr>
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<td><strong>Tis</strong> Carcinoma in situ</td>
<td><strong>Stage III</strong> T3a, b N0 M0</td>
</tr>
<tr>
<td><strong>T1</strong> Tumour invades subepithelial connective tissue</td>
<td><strong>Stage IV</strong> T4a N0 M0</td>
</tr>
<tr>
<td><strong>T2</strong> Tumour invades muscularis</td>
<td><strong>Any T</strong> N1, N2, N3 M0</td>
</tr>
<tr>
<td><strong>T3</strong> <em>(Renal pelvis)</em> Tumour invades beyond muscularis into peripelvic fat or renal parenchyma</td>
<td><strong>Any T</strong> Any N M1</td>
</tr>
<tr>
<td><em>(Ureter)</em> Tumour invades beyond muscularis into periureteric fat</td>
<td></td>
</tr>
<tr>
<td><strong>T4</strong> Tumour invades adjacent organs or through the kidney into perinephric fat</td>
<td></td>
</tr>
<tr>
<td><strong>N</strong> – Regional lymph nodes</td>
<td></td>
</tr>
<tr>
<td><strong>NX</strong> Regional lymph nodes cannot be assessed</td>
<td></td>
</tr>
<tr>
<td><strong>N0</strong> No regional lymph node metastasis</td>
<td></td>
</tr>
<tr>
<td><strong>N1</strong> Metastasis in a single lymph node 2 cm or less in greatest dimension</td>
<td></td>
</tr>
<tr>
<td><strong>N2</strong> Metastasis in a single lymph node node more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, none more than 5 cm in greatest dimension</td>
<td></td>
</tr>
<tr>
<td><strong>N3</strong> Metastasis in a lymph node more than 5 cm in greatest dimension</td>
<td></td>
</tr>
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</table>

1. (944,2662).
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## TNM classification of carcinomas of the urethra

<table>
<thead>
<tr>
<th>TNM classification</th>
<th>N – Regional lymph nodes</th>
<th>M – Distant metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>T – Primary tumour</td>
<td>NX Regional lymph nodes cannot be assessed</td>
<td>MX Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>TX Primary tumour cannot be assessed</td>
<td>N0 No regional lymph node metastasis</td>
<td>M0 No distant metastasis</td>
</tr>
<tr>
<td>T0 No evidence of primary tumour</td>
<td>N1 Metastasis in a single lymph node 2 cm or less in greatest dimension</td>
<td>M1 Distant metastasis</td>
</tr>
<tr>
<td>Urethra (male and female)</td>
<td>N2 Metastasis in a single lymph node more than 2 cm in greatest dimension, or multiple lymph nodes</td>
<td></td>
</tr>
<tr>
<td>Ta Non-invasive papillary, polypoid, or verrucous carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tis Carcinoma in situ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 Tumour invades subepithelial connective tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2 Tumour invades any of the following: corpus spongiosum, prostate, periurethral muscle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3 Tumour invades any of the following: corpus cavernosum, beyond prostatic capsule, anterior vagina, bladder neck</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4 Tumour invades other adjacent organs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urothelial carcinoma of prostate (prostatic urethra)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tis pu Carcinoma in situ, involvement of prostatic urethra</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tis pd Carcinoma in situ, involvement of prostatic ducts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>Ta N0 M0</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>T1 N0 M0</td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>T2 N0 M0</td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>T3 N0, N1 M0</td>
<td></td>
</tr>
</tbody>
</table>

1 ([044,2662]).

A help desk for specific questions about the TNM classification is available at [http://www.uicc.org/tnm/](http://www.uicc.org/tnm/).
Infiltrating urothelial carcinoma

**Definition**
Infiltrating urothelial carcinoma is defined as a urothelial tumour that invades beyond the basement membrane.

**ICD-O code**  8120/3

**Synonym**  Transitional cell carcinoma.

**Epidemiology of urothelial bladder cancer**
Bladder cancer is the 7th most common cancer worldwide, with an estimated 260,000 new cases occurring each year in men and 76,000 in women [749].

Cancer of the urinary bladder accounts for about 3.2% of all cancers worldwide and is considerably more common in males than in females (ratio worldwide is about 3.5:1) [2014]. In both sexes, the highest incidence rates of bladder cancer are observed in Western Europe, North America and Australia [2016].

The highest incidence rates of bladder cancer in males in 1990s were observed in the following registries: Limburg (Belgium) – 42.5/105, Genoa Province (Italy) – 41.1/105, and Mallorca (Spain) – 39.5/105 [2016]. The highest rates in females were noted in Harare (Zimbabwe) – 8.3/105, Scotland (UK) – 8.1/105, North Western England (UK) – 8.0/105, and white population of Connecticut (USA) – 8.0/105. The highest prevalence of bladder cancers in both males and females is observed in North America and in countries of the European Union [2084].

In general, among all registries included into the 8th volume of "Cancer Incidence in Five Continents" [2016] urothelial carcinoma constitutes 84% of bladder cancer in males and 79% in females. Other types of bladder cancer, i.e. squamous cell carcinoma and adenocarcinoma have much lower relative frequency. In all "Cancer Incidence in Five Continents" [2016] registries squamous cell carcinoma accounts for 1.1% and 2.8% of all bladder cancers in men and women respectively. Adenocarcinoma of the bladder constitutes respectively 1.5% and 1.9% of all bladder tumours worldwide [2016]. It is estimated that approximately 70-80% of patients with newly diagnosed bladder cancer present with non-invasive or early invasive (i.e. stage Ta, Tis, or T1).

**Etiology of urothelial bladder cancer**

**Risk factors**
There are several known and potential risk factors of bladder cancer. Cigarette smoking and occupational exposure to aromatic amines are the most important among them [1877].

**Tobacco smoking**
Tobacco smoking is the major established risk factor of bladder cancer. It is estimated that the risk of bladder cancer attributed to tobacco smoking is 66% for men and 30% for women [1158].

The risk of bladder cancer in smokers is 2-6 fold that of non-smokers [313, 391, 1877]. The risk increases with increasing duration of smoking, and for those with the longest history of smoking (60 years or more) reaches approximately 6 in men and 5 in women [313]. The excess of risk is observed also with increasing intensity of smoking (number of cigarettes per day), reaching maximum of about 3 for those smoking 40 or more cigarettes per day [313]. The increase of risk with the increasing duration and intensity of smoking is similar in both sexes [1158] but, some studies indicate higher risk in women than in men at the equivalent level of exposure [391].
The risk of bladder cancer goes down after stopping smoking, and 15 years cessation tends to be approximately that of non-smokers [1158]. The decrease of risk after cessation is similar in both sexes [391]. Glutathione S-transferase M1 (GSTM1) null status is associated with a modest increase in the risk of bladder cancer [700].

**Occupational exposure**

Bladder cancer is associated with a number of occupations or occupational exposures. The first such association was observed in 1895 by Rehn, who reported high rates of bladder cancer among men employed in the aniline dye industry [617]. Subsequent research among dyestuffs workers identified the aromatic amines benzidine and 2-naphthylamine, and possibly 1-naphthylamine, as bladder carcinogens [1150]. It has been estimated that contact with occupational carcinogens causes up to 25% of all bladder tumours [2025].

**Phenacetin**

Several epidemiological studies indicate that chronic abuse of analgesics containing phenacetin greatly enhance the risk of developing urothelial cancer of the renal pelvis, ureter and bladder. The relative risk has been estimated in the range of 2.4 to more than 6 [1150]. Early cases have been reported from Scandinavia [253,460], Switzerland [1729] and Australia [1668].

**Medicinal drugs**

The cytostatic agent, cyclophosphamide, has long been associated with the development of leukemia and lymphoma. In addition, treatment with cyclophosphamide has been reported to be associated with an increased risk of squamous cell carcinomas and sarcomas, especially leiomyosarcomas [1150, 2577]. Similarly, chlorophosphate is associated with the development of bladder cancer [2606].

**Chronic infections**

Chronic cystitis caused by *Schistosoma haematobium* is an established cause of bladder cancer. The resultant bladder tumours are usually squamous cell carcinomas. Some authors suggested association between bladder cancer and urinary tract infections and urinary tract stones.

The underlying mechanism may lead to chronic irritation of the bladder epithelium, which may increase bladder cancer risk.

**Arsenic**

Several studies showed that use of drinking water containing chlorination by-products or contaminated by arsenic may increase risk of bladder cancer [367,1117,1150,2444]. An IARC Monographs Working Group reviewed in 2004 the relevant epidemiological studies and concluded that arsenic in drinking-water is carcinogenic to humans (Group 1) and that there is sufficient evidence that it causes urinary bladder cancer. Key evidence came from ecological studies in Chile and Taiwan (China) where large populations were exposed [1157].

**Coffee**

There is no clear evidence of carcinogenic effect of coffee or caffeine in experimental animals [1151], but some epidemiological studies in humans showed increased risk in coffee drinkers as compared with non-coffee drinkers [1027]. A recent study showed increased risk of bladder cancer caused by coffee drinking only in never smokers, while no increase of risk was observed in ever smokers [2840].

**Artificial sweeteners**

There is no convincing evidence that artificial sweeteners (such as saccharin) play a role in the etiology of bladder cancer [1877]. The IARC currently classifies saccharin in group 3, i.e. not classifiable as to its carcinogenicity to humans [1155].

**Clinical features**

**Signs and symptoms**

The type and severity of clinical signs and symptoms of infiltrating urothelial carcinoma depends on the extent and location of the tumour. Most patients with urothelial tumours present with at least microscopic hematuria [1718]. The most common presenting symptom of bladder cancer is painless gross hematuria which occurs in 85% of patients [2713]. Subsequent clotting and
clinical signs of infiltrating tumours of the bladder. Microscopic hematuria may be the first symptom in 10% of patients with bladder tumours. Upper tract tumours occur in less than 1% of patients with bladder tumours, and the majority are candidates for potentially curative treatment. Infiltrative bladder tumours may be present in the case of extensive carcinoma in situ. Tumours infiltrating the ureteral orifice may lead to hydronephrosis, which is considered a poor prognostic sign. Rarely, patients with extensive disease present with a palpable pelvic mass or lower extremity oedema. In case of advanced disease weight loss or abdominal or bone pain may be present due to metastases.

Although diagnosis of a bladder neoplasm may sometimes be suspected on ultrasound or computed tomography scan, it is confirmed on cystoscopy. Histological diagnosis is secured by resecting the tumour deep into the muscular layer of the bladder wall. A fraction of patients with T1 disease may be treated by repeat transurethral resection alone. However, in case of extensive disease most patients are candidates for potentially curative treatment. Upper tract tumours occur in less than 10% of patients with bladder tumours. Microscopic hematuria may be the first clinical signs of infiltrating tumours of the renal pelvis and ureter and roughly half of the patients present with gross hematuria. In case of blood clotting obstruction may be acute and lead to painful ureteral colic and can be mistaken for ureterolithiasis. Hydronephrosis may also result but may go clinically unnoticed if obstruction develops slowly. In case of a single kidney or bilateral obstruction anuria and renal insufficiency result.

In case of suspected upper urinary tract tumour radiological imaging (intravenous urogram or computed tomography) or endoscopic examination is advised. Approximately two thirds of the tumours are located in the distal ureter. Standard treatment for upper tract tumours is nephroureterectomy including the ureteral orifice, which recently is also performed laparoscopically.

Primary infiltrating urothelial tumours of the urethra are rare. Conversely, approximately 15% of patients with carcinoma in situ of the bladder present with prostatic urethral involvement. Occasionally, recurrent tumour is found in the urethral stump after cystectomy. Bloody discharge from the urethra requires endoscopic examination and surgical resection if tumour is found.

**Imaging**

Various imaging modalities are used not only for detection but also for staging of infiltrating urothelial carcinoma. They include ultrasound, intravenous urography (IVU), computed tomography (CT) and magnetic resonance imaging (MRI). Transabdominal ultrasonography of the bladder is quick, non-invasive, inexpensive and available in most institutions. However, staging accuracy is less than 70% for infiltrating bladder tumours (598). Sensitivity reaches only 63%, yet with a specificity of 99% (554). There is a high false negative rate for ultrasound examination because of tumour location, obesity of the patient or postoperative changes. Transurethral ultrasonography may increase accuracy to >95% for T2 and T3 bladder tumours (1357). Endoureteric sonographic evaluation of ureteral and renal pelvic neoplasms is technically feasible (1515). However, as endoluminal sonography is invasive and examiner dependent it is not routinely used. Iliac lymph nodes cannot be assessed reliably on ultrasound.

While IVU is reliable in diagnosing intraluminal processes in ureter, pelvis and – with lesser accuracy – in bladder, it fails to detect the extent of extramural tumour. In addition IVU misses many extraluminal pathologic processes (such as renal mass) and, therefore, has increasingly been replaced by CT and MRI (96). In most institutions CT is used as a primary staging tool as it is more accessible and more cost effective than MRI. However, both CT and MRI scanning often fail to differentiate between post-transurethral resection oedema and tumour (168). Staging accuracy of CT has been described in the range of 55% for urothelial carcinoma in the urinary bladder (1997). Understaging of lymph node metastases in up to 40% and overstaging 6% of the cases are the major causes of error. Spiral CT has increased accuracy as breathing artefacts are diminished. Enhanced computing methods bear the potential to improve accuracy by transforming data into three dimensional images allowing for “virtual” endoscopy (765). MRI appears to be somewhat better to assess the depth of intramural invasion and extravesical tumour growth but does not exceed 83% (2454).

Unlike in other tumours diagnostic accuracy of positron emission tomography (PET) in patients with invasive carcinoma of the bladder is poor (1481).

**Fig. 2.03** Infiltrative urothelial carcinoma. A,B Ultrasound images of a solid bladder tumour. Bladder (black) with tumour (white) protruding into the lumen. C Multiple metastases (hot spots) of the bone.
**Tumour spread and staging**

**Urinary bladder**

*T category*

Cystoscopy provides a limited role in the staging process (468,1085,2302). Transurethral resection (TURB) of all visible lesions down to the base is required for accurate assessment of depth of tumour invasion. pT categorization in TURB allows for recognition of pT1 and pT2 disease but the definitive categorization requires examination of the cystectomy specimen. Tumour infiltrating muscle is not equivalent to muscularis propria invasion as small slender fascicles of muscle are frequently present in lamina propria (muscularis mucosae) (2203). Tumour infiltrating the adipose tissue is not always indicative of extravesical extension as fat may be normally present in all layers of the bladder wall (2069).

The impact of additional random biopsies remains unclear (751). In case of positive urine cytology without a visible lesion or evidence of upper urinary tract tumours random biopsies from different areas of the bladder wall are taken to detect Tis bladder cancer. Re-biopsy 1-6 weeks after the primary resection is most often performed in large pTa and all pT1 tumours (411,540, 645,1332,2323).

The role of intravenous pyelography for detecting simultaneous tumours of the upper urinary tract (UUT) and/or ureteral obstruction is controversial (63,901). The accuracy of imaging techniques (CT, MRI, PET) for determining the T-category is limited (234,394,1050,1997,2402, 2651,2864). Bimanual palpation to diagnose organ-exceeding tumours has lost its impact.

*N category*

The impact of CT and MRI (352,2740, 2746) has been investigated in numerous studies, however, sensitivity and specificity of these techniques remains limited. Nevertheless, lymph node enlargement is highly predictive of metastatic disease. The use of CT-guided needle biopsy of lymph nodes has been reported (239). Pelvic lymph node dissection up to the aortic bifurcation represents the state-of-art procedure. Furthermore, a potential therapeutic impact has been assigned to this procedure (2102,2732,2733). Modifications, i.e. sentinel lymph node resection or laparoscopic lymph node dissection for N-staging are considered experimental (686,2387).

*M category*

In muscle-invasive tumours lung X-ray and exclusion of liver metastases by imaging (ultrasound, CT, MRI) are required. Skeletal scintigraphy for the detection of bone metastases should be performed in symptomatic patients. In T1 disease, M-staging is recommended before cystectomy.

**Upper urinary tract tumours**

*T category*

T-staging of tumours of the upper urinary tract tumours is performed after radical surgery in the vast majority of cases or after endoscopical tumour resection. Imaging procedures (CT, MRI) may be of value (838,2089).

To identify simultaneous bladder tumours cystoscopy of these patients is mandatory (99,319).

*N category*

N-staging is performed by imaging techniques (CT, MRI) and by lymph node dissection (1349,1747,1750).

*M category*

Because of similarities with bladder tumours (552,1137), M-staging in upper urinary tract tumours follows the same rules.

**Prostatic and urethral urothelial tumours**

*T category*

T-staging of urothelial tumours of the prostate ducts or urethra is performed after biopsy or after radical surgery. Imaging procedures (CT, MRI) may be helpful (771).

Because of the coincidence of simultaneous bladder tumours cystoscopy of these patients is mandatory (99,119).

*N category*

N-staging is performed by imaging techniques (CT, MRI) or by lymph node dissection (542). Specifically for meatal or distal urethral tumours the inguinal region must be considered.

*M category*

In general, M-staging in urothelial tumours of the prostate or urethra follows the same rules as in bladder tumours.

**Macroscopy**

Infiltrative carcinomas grossly span a range from papillary, polypoid, nodular, solid, ulcerative or transmural diffuse growth. They may be solitary or multifocal. The remaining mucosa may be nor-
Carcinoma has no specific features and shows infiltrating cohesive nests of cells with moderate to abundant amphophilic cytoplasm and large hyperchromatic nuclei. In larger nests, palisading of nuclei may be seen at the edges of the nests. The nucleus is typically pleomorphic and often has irregular contours with angular profiles. Nucleoli are highly variable in number and appearance with some cells containing single or multiple small nucleoli and others having large eosinophilic nucleoli. Foci of marked pleomorphism may be seen, with bizarre and multinuclear tumour cells (293). Mitotic figures are common, with numerous abnormal forms. The invasive nests usually induce a desmoplastic stromal reaction which is occasionally pronounced and may mimic a malignant spindle cell component, a feature known as pseudosarcomatous stromal reaction (1555). In most cases, the stroma contains a lymphocytic infiltrate with a variable number of plasma cells. The inflammation is usually mild to moderate and focal, although it may be severe, dense, and widespread. Neutrophils and eosinophils are rarely prominent. Retraction clefts are often present around the nests of carcinoma cells, mimicking vascular invasion. It is important to be aware of this feature in order to avoid misinterpretation as vascular invasion. Foci of squamous and glandular differentiation are common, and should be reported (1554,2177,2276). Intraepithelial neoplasia including carcinoma in situ is common in the adjacent urothelium (1547,1552). Occasionally, mucoid cytoplasmic inclusions may be present.

Histologic variants
Urothelial carcinoma has a propensity for divergent differentiation with the most common being squamous followed by glandular. Virtually the whole spectrum of bladder cancer variants may be seen in variable proportions accompanying otherwise typical urothelial carcinoma. Divergent differentiation frequently parallels high grade and high stage urothelial cancer. When small cell differentiation is present, even focally, it portends a poor prognosis and has different therapeutic ramifications, and hence should be diagnosed as small cell carcinoma.

Infiltrating urothelial carcinoma with squamous differentiation
Squamous differentiation, defined by the presence of intercellular bridges or keratinization, occurs in 21% of urothelial carcinomas of the bladder, and in 44% of tumours of the renal pelvis (1554,1637). Its frequency increases with grade and stage (1554). Detailed histologic maps of urothelial carcinoma with squamous differentiation have shown that the proportion of the squamous component may vary considerably, with some cases having urothelial carcinoma in situ as the only urothelial component (2276). The diagnosis of squamous cell carcinoma is reserved for pure lesions without any associated urothelial component, including urothelial carcinoma in situ (2177). Tumours with any identifiable urothelial element are classified as urothelial carcinoma with squamous differentiation (1554,2177) and an estimate of the percentage of squamous component should be provided. Squamous differentiation may show basaloid or clear cell features. Cytokeratin 14 and L1 antigen have been reported as immunohistochemical markers of squamous differentiation (1025,2655). Uroplakins, are expressed in urothelial carcinoma and not in squamous differentiation (2848).

Histology
The histology of infiltrating urothelial carcinoma is variable (80,293,944). Most of pT1 cancers are papillary, low or high grade, whereas most pT2-T4 carcinomas are non-papillary and high grade. These carcinomas are graded as low grade and high grade depending upon the degree of nuclear anaplasia and some architectural abnormalities (706,1548,1798). Some cases may show relatively bland cytology (2896).

The most important element in pathologic evaluation of urothelial cancer is recognition of the presence and extent of invasion (293). In early invasive urothelial carcinomas (pT1), foci of invasion are characterized by nests, clusters, or single cells within the papillary cores and/or lamina propria. It is recommended that the extent of lamina propria invasion in pT1 tumours should be stated (706). The depth of lamina propria invasion is regarded as a prognostic parameter in pT1 cancer. Morphologic criteria useful in assessing lamina propria invasion include the presence of desmoplastic stromal response, tumour cells within the retraction spaces, and paradoxical differentiation (invasive nests of cells with abundant eosinophilic cytoplasm at the advancing edge of infiltration (2117)). Recognition of invasion may be problematic because of tangential sectioning, thermal and mechanical injury, marked inflammatory infiltrate obscuring neoplastic cells and inverted or broad front growth (78). Thermal artefact can also hamper the interpretation of muscularis propria invasion.

Histopathology
The histology of infiltrating urothelial carcinoma in situ.

Infiltrating urothelial carcinoma

Fig. 2.05 Infiltrative urothelial carcinoma. CT image of a solid bladder tumour protruding into the lumen.

Fig. 2.06 Infiltrative urothelial carcinoma (stage T1). A Early tumour invasion into papillary stalk (H&E). B Immunohistochemistry with anticytokeratin may aid in establishing early tumour invasion.

Infiltrating urothelial carcinoma
feature in such patients undergoing radical cystectomy, possibly, because of its association with high grade tumours (336). Squamous differentiation was predictive of a poor response to radiation therapy and possibly also to systemic chemotherapy (336,1637,2276).

**Infiltrating urothelial carcinoma with glandular differentiation**

Glandular differentiation is less common than squamous differentiation and may be present in about 6% of urothelial carcinomas of the bladder (1554). Glandular differentiation is defined as the presence of true glandular spaces within the tumour. These may be tubular or enteric glands with mucin secretion. A colloid-mucinous pattern characterized by nests of cells “floating” in extracellular mucin occasionally with signet ring cells may be present (1554). Pseudoglandular spaces caused by necrosis or artefact should not be considered evidence of glandular differentiation. Cytoplasmic mucin containing cells are present in 14-63% of typical urothelial carcinoma and are not considered to represent glandular differentiation (633). The diagnosis of adenocarcinoma is reserved for pure tumours (2177). A tumour with mixed glandular and urothelial differentiation is classified as urothelial carcinoma with glandular differentiation (923) and an estimate of the percentage of glandular component should be provided. The expression of MUC5AC-apomucin may be useful as immunohistochemical marker of glandular differentiation in urothelial tumours (1408).

![Image](image1)

**Fig. 2.07 A,B** Infiltrative urothelial carcinoma. Early invasion not reaching muscularis mucosae (pT1a).

![Image](image2)

**Fig. 2.08 A,B** Infiltrative urothelial carcinoma. The infiltration of lamina propria goes beyond the muscularis mucosae (pT1b).

![Image](image3)

**Fig. 2.09** Infiltrative urothelial carcinoma. **A** Invasive urothelial carcinoma grade 3. **B** Islands of high grade urothelial carcinoma extending through the muscularis propria (detrusor muscle).
The clinical significance of glandular differentiation and mucin positivity in urothelial carcinoma remains uncertain (1528).

**Nested variant**
The nested variant of urothelial carcinoma is an aggressive neoplasm with less than 50 reported cases (639, 1109, 1848, 2562, 2896). There is a marked male predominance (639), and 70% of patients died 4-40 months after diagnosis, in spite of therapy (1109). This rare pattern of urothelial carcinoma was first described as a tumour with a “deceptively benign” appearance that closely resembles Brunn nests infiltrating the lamina propria. Some nests have small tubular lumens (2562, 2896). Nuclei generally show little or no atypia, but invariably the tumour contains foci of unequivocal anaplastic cells exhibiting enlarged nucleoli and coarse nuclear chromatin (639, 1848). This feature is most apparent in deeper aspects of the tumour (1848).

Useful features in recognizing this lesion as malignant are the tendency for increasing cellular anaplasia in the deeper aspects of the lesion, its infiltrative nature, and the frequent presence of muscle invasion. The differential diagnosis of the nested variant of urothelial carcinoma includes prominent Brunn nests, cystitis cystica and glandularis, inverted papilloma, nephrogenic metaplasia, carcinoid tumour, paraganglionic tissue and paragangioma (639, 1109, 1848, 2562, 2896). The presence of deep invasion is most useful in distinguishing carcinoma from benign proliferations, and the nuclear atypia, which is occasionally present is also of value. Closely packed and irregularly distributed small tumour cells favour carcinoma. Inverted papilloma lacks a nested architecture. Nephrogenic metaplasia typically has a mixed pattern, including tubular, papillary, and other components, and only rarely has deep muscle invasion (639).

The nested variant of carcinoma may mimic paraganglioma, but the prominent vascular network of paraganglioma, which surrounds individual nests, is not usually present in nested carcinoma.

**Microcystic variant**
Occasionally urothelial carcinomas show a striking cystic pattern with cysts ranging from microscopic up to 1-2 mm in diameter. The cysts are round to oval, sometimes elongated and may contain necrotic material or pale pink secretions. The cyst lining may be absent, flattened or urothelial and may show the differentiation towards mucinous cells. The differential diagnosis therefore includes urothelial carcinoma with gland like lumina, as well as benign processes like cystitis cystica, cystitis glandularis or even nephrogenic adenoma. The pattern should be separated from the nested variant of urothelial carcinoma with tubular differentiation. Urothelial carcinoma

![Fig. 2.10 A,B Nested cell variant of urothelial carcinoma of the urinary bladder.](image)

![Fig. 2.11 A, B Infiltrative urothelial carcinoma. Nested variant.](image)
with microcystic pattern is unrelated to primary adenocarcinoma of the urinary bladder (656,1480,2891).

**Micropapillary variant**

Micropapillary bladder carcinoma is a distinct variant of urothelial carcinoma that resembles papillary serous carcinoma of the ovary, and approximately 60 cases were reported in the literature (81,1228,1558,1622,1941,2876). There is a male predominance and patients age range from fifth to the ninth decade with a mean age of 66 years. The most common presenting symptom is hematuria. Histologically, micropapillary growth pattern is almost always associated with conventional urothelial carcinoma or rarely with adenocarcinoma. The micropapillary pattern exhibits two distinct morphologic features. Slender-delicately papillary and filiform processes, often with a central vascular core, are observed on the surface of the tumours: on cross sections they exhibit a glomeruloid appearance. In contrast, the invasive portion is characterized by tiny nests of cells or slender papillae, which are contained within tissue retraction spaces that simulate lymphatic spaces. However, in most cases vascular/lymphatic invasion is present. The individual cells of micropapillary carcinoma show nuclei with prominent nucleoli and irregular distribution of the chromatin. Also, the cytoplasm is abundant, eosinophilic or clear, and mitotic figures range from few to numerous. Although the nuclear grade is frequently high, a few micropapillary carcinomas may appear deceptively low grade (81).

Immunohistochemical studies in one large series disclosed immunoreactivity of the micropapillary carcinoma in 20 of 20 cases for EMA, cytokeratin (CK) 7, CK 20, and Leu M1. CEA was positive in 13 of 20 cases (1228). Other markers including CA-125 antigen, B72.3, BerEp4, placental alkaline phosphatase immunoreacted in less than one third of the cases (1228). Psammoma bodies are infrequent. The tumours are invariably muscle invasive and this histology is often retained in the histology of metastases. Image analysis shows aneuploidy. Micropapillary carcinoma is a high grade, high stage variant of urothelial cancer with high incidence of metastases and morbidity. The presence of a micropapillary surface component or lamina propria invasive tumour without muscularis propria invasion in the specimen should prompt suggestion for rebiopsy because of the high association of muscularis propria invasion. Awareness of the micropapillary histology is important when dealing with metastases of unknown primary. Urothelial carcinoma with micropapillary component must be considered as a primary especially in males and women with normal gynecologic examination (81,1228).

**Lymphoepithelioma-like carcinoma**

Carcinoma that histologically resembles lymphoepithelioma of the nasopharynx has recently been described in the urinary bladder, with fewer than 40 cases reported (1106,1553). These tumours are more common in men than in women (10:3, ratio) and occur in late adulthood (range: 52-81 years, mean 69 years). Most patients present with hematuria and are stage T2-T3 at diagnosis (1106, 1553).
The etiopathogenesis of this tumour is unknown, although it is suspected that it originates from modified urothelial cells, that are possibly derived from basal (stem) cells [1106]. Hybridization with Epstein-Barr virus encoded RNA has been reported to be consistently negative in different series [82,973,1106,1553]. The tumour is solitary and usually involves the dome, posterior wall, or trigone, often with a sessile growth pattern.

Lymphoepithelioma-like carcinoma may be pure, predominant or focally admixed with typical urothelial carcinoma, or in some cases with squamous cell carcinoma or adenocarcinoma [1106,1553]. The proportion of lymphoepithelioma-like carcinoma histology should be provided in tumours with mixed histology. Histologically, the tumour is composed of nests, sheets, and cords of undifferentiated cells with large pleomorphic nuclei and prominent nucleoli. The cytoplasmic borders are poorly defined imparting a syncytial appearance. The background consists of a prominent lymphoid stroma that includes T and B lymphocytes, plasma cells, histiocytes, and occasional neutrophils or eosinophils, the latter being prominent in rare cases.

Carcinoma in situ elsewhere in the bladder is rarely present.

The epithelial cells of this tumour stain with several cytokeratin (CK) markers as follows: AE1/AE3, CK8, CK 7, and they are rarely positive for CK20 [1106,1553]. In some cases, it is possible to overlook the malignant cells in the background of inflamed bladder wall and misdiagnose the condition as florid chronic cystitis [1553]. The major differential diagnostic considerations are poorly differentiated urothelial carcinoma with lymphoid stroma; poorly differentiated squamous cell carcinoma, and lymphoma [1553]. The presence of recognizable urothelial or squamous cell carcinoma does not exclude lymphoepithelioma-like carcinoma; rather, the diagnosis is based on finding areas typical of lymphoepithelioma-like carcinoma reminiscent of that in the nasopharynx. Differentiation from lymphoma may be difficult, but the presence of a syncytial pattern of large malignant cells with a dense polymorphous lymphoid background is an important clue [1553].

Most reported cases of the urinary bladder had a relatively favourable prognosis when pure or predominant, but when lymphoepithelioma-like carcinoma is focally present in an otherwise typical urothelial carcinoma, these patients behave like patients with conventional urothelial carcinoma alone of the same grade and stage [1106,1553]. Some examples of lymphoepithelioma-like carcinoma have been described in the ureter and the renal pelvis [820,2224]. This tumour, thus far has been found to be responsive to chemotherapy when it is encountered in its pure form [82,623]. Experience at one institution has shown a complete response to chemotherapy and transurethral resection of the bladder [82,623]. Another series of nine patients treated with a combination of transurethral resection, partial or complete cystectomy, and radiotherapy disclosed four patients without evidence of disease, three who died of their disease and two who died of other causes [1106].

**Lymphoma-like and plasmacytoid variants**

The lymphoma-like and plasmacytoid variants of urothelial carcinoma are those in which the malignant cells resemble those of malignant lymphoma or plasmacytoma [1618,2272,2571,2933,2949]. Less than 10 cases have been reported. The histologic features of the lymphoma-like and plasmacytoid variants of urothelial carcinoma are characterized by the presence of single malignant cells in a loose or myxoid stroma. The tumour cells have clear or eosinophilic cytoplasm and eccentrically placed, enlarged hyperchromatic nuclei with small nucleoli. Almost all of the reported cases have had a component of high grade urothelial carcinoma in addition to the single malignant cells. In some of the cases, the single-cell component was predominant on the initial biopsy, leading to the differential diagnosis of lymphoma/plasmacytoma. The tumour cells stain with cytokeratin (CK) cocktail, CK 7 and (in some cases) CK 20 [2571]. Immunohistochemical stains for lymphoid markers have consistently been reported as negative.

Each of these variants of urothelial carcinoma may cause a significant differential diagnostic dilemma, especially in cases in which it constitutes the predominant or
exclusive component in a small biopsy sample. The importance of recognizing these variants lies in not mistaking them as a lymphoma or plasmacytoma. Limited information is available about the outcome of patients with these variants of urothelial carcinoma. Of 6 cases reported by Tamboli et al. (2571) 4 died of their disease, one died post-operatively and one is alive without evidence of disease.

**Sarcomatoid variant**

*w ith/without heterologous elements*

The term sarcomatoid variant of urothelial carcinoma should be used for all biphasic malignant neoplasms exhibiting morphologic and/or immunohistochemical evidence of epithelial and mesenchymal differentiation (with the presence or absence of heterologous elements acknowledged in the diagnosis). There is considerable confusion and disagreement in the literature regarding nomenclature and histogenesis of these tumours. In some series, both carcinosarcoma and sarcomatoid carcinoma are included as "sarcomatoid carcinoma" (2175). In others they are regarded as separate entities.

The mean age is 66 years (range, 50-77 years old) and most patients present with hematuria (1555,2175). A previous history of carcinoma treated by radiation or the exposition to cyclophosphamide therapy is common (1551). Rare examples of carcinosarcoma and sarcomatoid carcinomas have been described in the ureter and the renal pelvis (1549). The gross appearance is characteristically "sarcoma-like", dull grey with infiltrative margins. The tumours are often polypoid with large intraluminal masses. Microscopically, sarcomatoid carcinoma is composed of urothelial, glandular or small cell component showing variable degrees of differentiation (1555). A small subset of sarcomatoid carcinoma may have a prominent myxoid stroma (1238). The mesenchymal component most frequently observed is an undifferentiated high grade spindle cell neoplasm. The most common heterologous element is osteosarcoma followed by chondrosarcoma, rhabdomyosarcoma, leiomyosarcoma, liposarcoma angiosarcoma or multiple types of heterologous differentiation may be present (957,1238,1549,1555,2175). By immunohistochemistry, epithelial elements react with cytokeratins, whereas stromal elements react with vimentin or specific markers corresponding to the mesenchymal differentiation. The sarcomatoid phenotype retains the epithelial nature of the cells by immunohistochemistry or electronmicroscopy (1549,1555). Recent molecular studies, strongly argue for a monoclonal origin of both components (957). The cytological atypia of sarcomatoid carcinoma excludes non-neoplastic lesions such as the postoperative spindle cell nodule and inflammatory pseudotumour (1161,1550). Sarcomatoid carcinoma should be distinguished from the rare carcinoma with metaplastic, benign-appearing bone or cartilage in the stroma or those showing other pseudosarcomatous stromal reactions. Nodal and distant organ metastases at diagnosis are common (957,1555,1960,2175) and 70% of patients died of cancer at 1 to 48 months (mean 17 months) (1555).

**Urothelial carcinoma with giant cells**

High grade urothelial carcinoma may contain epithelial tumour giant cells or the tumour may appear undifferentiated resembling giant cell carcinoma of the lung. This variant is very infrequent. It must be distinguished from occasional cases showing giant cells (osteoclastic or foreign body type) in the stroma or urothelial carcinoma showing trophoblastic differentiation. In some cases the giant cell reaction is so extensive that it may mimic giant cell tumour of the bone (2948).
Urothelial carcinoma with trophoblastic differentiation

Trophoblastic differentiation in urothelial carcinoma occurs at different levels. High grade invasive urothelial carcinomas may express ectopic human chorionic gonadotropin (HCG) and other placental glycoproteins at the immunohistochemical level only or may contain numerous syncytiotrophoblastic giant cells [365,656,925,2891]. Very rarely, choriocarcinomatous differentiation has been reported.

Clear cell variant

The clear cell variant of urothelial carcinoma is defined by a clear cell pattern with glycogen-rich cytoplasm [1365, 1954]. The clear cell pattern may be focal or extensive and awareness of this pattern is important in differential diagnosis with clear cell adenocarcinoma of the urinary bladder and metastatic carcinoma from the kidney and prostate. The pattern may be seen in typical papillary or in situ lesions, but is relatively more common in poorly differentiated urothelial carcinomas.

Lipid-cell variant

Very infrequently urothelial carcinomas contain abundant lipid in which lipid distended cells mimic signet ring cell adenocarcinoma [1798]. The differential diagnosis is typical liposarcoma and signet ring cell carcinoma.

Undifferentiated carcinoma

This category contains tumours that cannot be otherwise classified. In our experience, they are extremely rare. Earlier the literature has included small cell carcinoma, giant cell carcinoma, and lymphoepithelioma-like carcinoma in this category, but these tumours are now recognized as specific tumour variants [656,1553]. Large cell undifferentiated carcinoma as in the lung is rare in the urinary tract, and those with neuroendocrine features should be recognized as a specific tumour variant [2816].

Genetic susceptibility

Urothelial carcinoma is not considered to be a familial disease. However numerous reports have described families with multiple cases [1313,1669]. There is strong evidence for an increased risk of ureteral and renal pelvic urothelial carcinomas, but not bladder cancers, in families with hereditary nonpolyposis colon cancer [2411,2789]. In addition several epidemiological studies showed that urothelial carcinomas have a familial component with a 1.5 to 2-fold increased risk among first-degree relatives of patients [23,905,1312,1387]. The only constitutional genetic aberration demonstrated so far in a family with urothelial carcinomas in two generation was a t(5;20)(p15;q11) balanced translocation [2336]. No chro-
mosomal alterations were found in 30 additional families with at least 2 affected individuals [22]. Interestingly, patients with sporadic urothelial carcinomas revealed a higher mutagen sensitivity than controls whereas patients with hereditary bladder cancer demonstrated no increased mutagen sensitivity [21]. A small increase in bladder cancer risk was demonstrated for polymorphic variants of several detoxifying enzymes, like NAT2 and GSTM1 [700,1624].

Somatic genetics
The genetic studies to date have used tumours classified according to WHO Tumours Classification (1973) and further studies are underway to link available genetic information to the current classification. It is assumed that invasive urothelial cancers are mostly derived from either non-invasive high grade papillary urothelial carcinoma (pTaG3) or urothelial carcinoma in situ. On the genetic level invasively growing urothelial cancer (stage pT1-4) is highly different from low grade non-invasive papillary tumours (Papillary Urothelial Neoplasm of Low Malignant Potential, Non-Invasive Low Grade Papillary Urothelial Carcinoma).

Chromosomal abnormalities
Invasively growing urothelial bladder cancer is characterized by presence of a high number of genetic alterations involving multiple different chromosomal regions. Studies using comparative genomic hybridization (CGH) have described an average of 7-10 alterations in invasive bladder cancer [2188,2189,2191,2418,2419]. The most frequently observed gains and losses of chromosomal regions are separately summarized for cytogenetic, CGH, and LOH (loss of heterozygosity). Taken together, the data highlight losses of 2q, 5q, 8p, 9p, 9q, 10q, 11p, 18q and the Y chromosome as well as gains of 1q, 5p, 8q, and 17q as most consistent cytogenetic changes in these tumours. The large size of most aberrations detected by CGH or cytogenetics makes

Fig. 2.19 A Infiltrative urothelial carcinoma. Urothelial carcinoma with trophoblastic differentia-

Fig. 2.20 Infiltrative urothelial carcinoma. A Clear cell variant of urothelial carcinoma of the urinary bladder. B Clear cell variant of urothelial carcinoma of the urinary bladder.

Fig. 2.21 Infiltrative urothelial carcinoma. A, B Urothelial carcinoma, lipoid cell variant showing the characteristic lipoblast-like features of proliferating cells (H&E). C Urothelial carcinoma, lipoid cell variant with immunohistochemical expression of cytokeratin 7 in most proliferating cells. D Urothelial carcinoma, lipoid cell variant with immunohistochemical expression of epithelial membrane antigen.
it difficult to identify genes leading to a selective growth advantage. The most important genes for bladder cancer development and progression remain to be discovered. Importantly, co-amplification and simultaneous overexpression of multiple adjacent oncogenes is often seen. For example, amplification of CCND1 at 11q13 can be accompanied by amplification of FGF4/FGF3 in 88% (R. Simon, personal communication), MDM2 amplification at 12q15 is accompanied by CDK4 amplification in 11% (2422), and HER2 amplification at 17q23 includes TOP2A in 15%. Simultaneous overexpression of two or more adjacent genes may provide cells with a significant growth advantage.

Oncogenes

Her2/neu is a transmembrane receptor tyrosine kinase without a known ligand. Its activation occurs through interaction with other members of the EGFR gene family. HER2 has regained considerable interest as the protein is the molecular target of trastuzumab (Herceptin®) therapy in breast cancer. HER2 is amplified in 10-20% and overexpressed in 10-50% of invasively growing bladder cancers (279,1397). H-ras mutations and 61% (1484). Depending on the method of detection, H-ras mutations have been reported in up to 45% of bladder cancers, without clear cut associations to tumour stage or grade (395,533, 772,1339,1341,1980).

H-ras is the only member of the ras gene family with known importance in urinary bladder cancer (279,1397). H-ras mutations are almost always confined to specific alterations within the codons 12, 13, and 61 (1484). Depending on the method of detection, H-ras mutations have been reported in up to 45% of bladder cancers, without clear cut associations to tumour stage or grade (395,533, 772,1339,1341,1980).

Table 2.02

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1 Average frequency from 45 bladder cancers from references (131,132,148,216,886,889,1388,1731,2030,2289,4411,2639,2709,2710).
2 Only large studies on invasive tumours (pT1-pT4; >50 analyzed tumours) included.

The epidermal growth factor receptor (EGFR) is another member of the class I receptor family. EGFR is a transmembrane tyrosine kinase acting as a receptor for several ligands including epidermal growth factor (EGF) and transforming growth factor alpha. EGFR also serves as a therapeutic target for several drugs including small inhibitory molecules and antibodies. EGFR is amplified in 3-5% and overexpressed in 30-50% of invasively growing bladder cancers (217, 457,914,1510,1690,2305,2844).

Cyclin dependent kinases (CDKs) and their regulatory subunits, the cyclins, are important promoters of the cell cycle. The cyclin D1 gene (CCND1) located at 11q13 is one of the most frequently amplified and overexpressed oncogenes in bladder cancer. About 10-20% of bladder cancers show gene amplification (322,983,2114,2308), and overexpression has been reported in 30-50% of tumours (1464,1991,2371,2394,2762). Some investigators found associations between CCND1 expression and tumour recurrence and progression or patient survival (1984,2371,2394), but these data were not confirmed by others (1517,2540,2762).

The MDM2 gene, located at 12q14.3-q15, codes for more than 40 different splice variants, only two of which interact with TP53 and thereby inhibit its ability to activate transcription (173). Conversely, the transcription of MDM2 is induced by wild type TP53. In normal cells this autoregulatory feedback loop regulates TP53 activity and MDM2 expression. MDM2 also promotes TP53 protein degradation, making MDM2 overexpression an alternate mechanism for TP53 inactivation. MDM2 amplification is frequent in human sarcomas (1270), but it occurs in only 4-6% of invasively growing bladder cancers (983,2422). MDM2 amplification was unrelated to patient prognosis in one study (2422). Detectable MDM2 protein expression has been reported in 10-40% of bladder cancers, but there is disagreement about associations to tumour stage and grade between the studies (1172,1206, 1358,1495,2067, 2068,2330, 2390).
expression or inactivation are summarized below. The TP53 gene, located at 17q23, encodes a 53kDa protein which plays a role in several cellular processes including cell cycle, response to DNA damage, cell death, and neovascularization (1089). Its gene product regulates the expression of multiple different genes (2757). Mutations of the TP53 gene, mostly located in the central, DNA binding portion of the gene, are a hallmark of invasively growing bladder cancers. An online query of the International Agency for Research on Cancer (IARC) database (R7 version, September 2002) at www.iarc.fr/P53/ (1957) revealed TP53 mutations in 40-60% (1569, 2619) of invasive bladder cancers (in studies investigating at least 30 tumours). Although there are no specific mutational hotspots, more than 90% of mutations have been found in exons 4-9. Often TP53 mutations can be detected immunohistochemically.

Fig. 2.22 Putative model of bladder cancer development and progression based on genetic findings. Thick arrows indicate the most frequent pathways, dotted lines the most rare events. The typical genetic alterations in genetically stable and unstable tumours are described in the text.

Fig. 2.23 Infiltrative urothelial carcinoma. FISH analysis of a human metaphase chromosome spread showing locus specific hybridization signals for the telomeric (green signals) and the centromeric (red signals) regions of chromosome 1. The chromosomes have been counterstained with 4,6-Diamidino-2-phenylindol (DAPI).

Fig. 2.24 Invasive urothelial cancer. FISH analysis shows two copies of centromere 17 (red) and more than 30 copies of the HER2 gene (green) reflecting HER2 gene amplification.

Fig. 2.25 Infiltrative urothelial carcinoma. Contribution of several oncogenes in cellular signalling pathways.
since many TP53 mutations lead to protein stabilization resulting in nuclear TP53 accumulation. Immunohistochemical TP53 analysis has practical utility in surgical pathology. In addition to a postulated role as a prognostic marker, immunohistochemical TP53 positivity is a strong argument for the presence of genetically unstable neoplasia in cases with questionable morphology.

The PTEN (phosphatase and tensin homology) gene also known as MMAC1 (mutated in multiple advanced cancers) and TEP1 (TGFbeta regulated and epithelial cell enriched phosphatase) is a candidate tumour suppressor gene located at chromosome 10q23.3. The relative high frequency (20-30%) of LOH at 10q23 in muscle invasive bladder cancer (1256) would make PTEN a good tumour suppressor candidate. However, the frequency of PTEN mutations is not clear at present. In three technically well performed studies including 35, 63, and 345 tumour samples, mutations were detected in 0%, 0.6%, and 17% of cases (141, 359,2776). These results leave the question for the predominant mechanism of inactivation of the second allele open, or indicate that PTEN is not the (only) target gene at 10q23.

The retinoblastoma (RB1) gene product was the first tumour suppressor gene to be identified in human cancer. RB1 which is localized at 13q14, plays a crucial role in the regulation of the cell cycle. Inactivation of RB1 occurs in 30-80% of muscle invasive bladder cancers (360,1177,2110,2112). Some investigators have reported an association between altered Rb expression and reduced patient survival (498,1530). Alterations of DNA repair genes are important for many cancer types. In invasive bladder cancer, alterations of mismatch repair genes (mutator phenotype) are rare. A metaanalysis of 7 studies revealed that microsatellite instability (MSI) was found only in 12 of 524 (2.2%) of cases suggesting that MSI does not significantly contribute to bladder cancer development (1032).

The genes encoding p16 (CDKN2A) and p15 (CDKN2B) map to chromosome 9p21, a site that is frequently involved in heterozygous and homozygous deletions in urinary bladder cancer of all types. Alterations of 9p21 and p15/p16 belong to the few genetic alterations that are equally frequent or even more frequent in non-invasive low grade neoplasms than in invasively growing/high grade tumours.

**Prognostic and predictive factors**

**Clinical factors**

In general, individual prognosis of infiltrating bladder tumours can be poorly predicted based on clinical factors alone. Tumour multifocality, tumour size of >3 cm, and concurrent carcinoma in situ have been identified as risk factors for recurrence and progression (2215). Tumour extension beyond the bladder on bimanual examination, infiltration of the ureteral orifice (999), lymph node metastases and presence of systemic dissemination are associated with a poor prognosis.

**Morphologic factors**

Morphologic prognostic factors include grade, stage, as well as other specific morphologic features. Histologic grade probably has prognostic importance for pT1 tumours. As most pT2 and higher stage tumours are high grade, its value as an independent prognostic marker remains questionable. Depth of invasion, which forms the basis of pT categorization is the most important prognostic factor. In efforts to stratify category pT1 tumours further, sub-stag-
Tumours of the urinary system

Invasion systems have been proposed on the basis of the level of invasion into the lamina propria. Tumours that infiltrate beyond the muscularis mucosae have a higher progression rate (1039, 2886). An alternative is to stratify patients according to the level of invasion into lamina propria measured by a micrometer attached to the microscope (435, 2562). Stage T1 is frequently found in tumours of high grade, and stage T1 tumours that are high grade (1798) have a recurrence rate of 80%, 60% progression, and 35% 10-year survival rate.

Carcinoma in situ is more frequent with increasing grade and stage of the associated tumour, and carcinoma in situ with micro-invasion seems to increase the probability of aggressive behaviour (1547). Lymphatic and/or vascular invasion is associated with decreased survival in pT1 tumours (44% 5-year survival). Because vascular invasion is frequently overdiagnosed the prognostic significance of that factor remains uncertain (1436). Specific subtypes or histologic variants of urothelial carcinomas such as small cell carcinoma, sarcomatoid carcinoma, nested variant, micro-papillary carcinoma, and lymphoepitheliomma-like carcinoma may be clinically relevant in patient’s prognosis. Margin status after cystectomy is also an important predictor of prognosis.

The pattern of tumour growth has been suggested to be important; a pushing front of invasion had a more favourable prognosis than tentacular invasion in few studies (1226, 1798).

Genetic factors

Despite marked differences in the prognosis of pT1 and pT2-4 cancers, these tumours are highly similar on the genetic level (2188, 2419). It could therefore be expected, that similar genetic alterations might be prognostically relevant in all stages. A multitude of molecular features has been analyzed for a possible prog-

<table>
<thead>
<tr>
<th>Amplicon</th>
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<th>Amplification frequency *</th>
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Table 2.03

Amplification sites in invasive bladder cancer.

Only studies with more than 20 patients are included. If one amplicon was detected only in a single study with less than 20 tumours, the number of amplified cases is given in relation to the total number of analyzed tumours. Capital letters in brackets indicate the method of analysis: (C) = CGH; (F) = FISH; (S) = Southern blotting; (P) = PCR; (K) = Karyotyping.

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nostic role in invasively growing bladder cancer [1287,2496,2620]. Despite all this extensive research, there is currently no molecular parameter that is sufficiently validated and has sufficient predictive power to have accepted clinical value in these tumours.

TP53 Alterations of the TP53 tumour suppressor gene have been by far the most intensively studied potential prognostic marker [2329]. Early studies suggested a strong prognostic importance of immunohistochemically detectable nuclear TP53 protein accumulation in both pT1 [963,2295] and pT2-4 cancers [725], and TP53 analysis was close to routine application in urinary bladder cancer [1980]. However, many subsequent studies could not confirm these data [777, 1494,2064]. It is possible that part of these discrepancies are due to different response rates to specific therapy regimens for tumours with and without TP53 alterations [505,1421,2293]. A recent metaanalysis of more than 3700 tumours found a weak but significant association between TP53 positivity and poor prognosis [2329]. An independent prognostic role of TP53 alterations was only found in 2 out of 7 trials investigating pT2-4 cancer. TP53 alterations may be clinically more important in pT1 cancer, since more than 50% of these studies found independent prognostic significance. However, it cannot be excluded that a fraction of overstaged TP53 negative pTa tumours with good prognosis has contributed to some of these results [2306]. Overall, it appears that 1) TP53 alterations do not sufficiently well discriminate good and poor prognosis groups in properly staged bladder cancers to have clinical utility, and 2) currently used methods for immunohistochemical TP53 analysis are not reliable enough for clinically useful measurement of TP53 alterations.

Cell cycle regulation p21 and p27 inhibit or stimulate cyclin dependent kinases. Stein et al. [2495] showed in a series of 242 invasive cancers treated by cystectomy that TP53+/p21- tumours were associated with worst prognosis compared to those with TP53+/p21+ phenotype. A similar result was obtained by Qureshi et al. [2126] in a series of 68 muscle invasive non-metastatic tumours treated with radical radiotherapy. The expression of p27 protein was a striking predictor of prognosis in a set of patients treated by cystectomy and adjuvant chemotherapy [2620]. A 60% long term survival was observed in 25 patients with p27+ tumours as compared to 0% of patients with p27- tumours. No survival difference between p27 positive and negative tumours was observed in the same study in patients that had not received adjuvant chemotherapy [2620]. Inactivation of the retinoblastoma (RB) gene occurs in 30-80% of bladder cancers [360,1172,1530,2845], most frequently as a consequence of heterozygous 13q deletions in combination with mutation of the remaining allele [497]. Several investigators reported an association between altered Rb expression and reduced patient survival in muscle invasive cancers [498,504,1530] and with tumour progression in pT1 carcinomas [963]. Others could not confirm these results [1207,1359,2095]. HER2 overexpression occurs in 30-70% of invasive bladder cancers. Some studies suggested that HER2 expression is a predictor for patient survival or metastatic growth [1358,1534,1787,2301] but these associations were not confirmed by others [1509,1708,2675]. Gandour-Edwards et al. recently described an intriguing link between Her2 expression and improved survival after paclitaxel-based chemotherapy [832]. Co-amplification and co-expression of the adjacent topoisomerase 2 alpha (TOP2A) may also play a role for an altered chemosensitivity of HER-2 amplified tumours [1209, 1210]. EGFR is overexpressed in 30-50% of invasively growing bladder cancers [217,457,914,1510,1890,2305,2844]. Early reports linked EGFR expression to an increased risk for tumour recurrence and progression, as well as to reduced survival [1717,1875,1876]. In one study with 212 patients, EGFR expression was even found to be an independent predictor of progression and survival [1709], but later studies could not confirm these results [2152,2475,2611,2748].

Angiogenesis The extent of angiogenesis can be quantitated by immunostaining microvessels using antibodies against factor VIII or CD34. At least one study has suggested microvessel density as an independent prognostic factor in muscle invasive bladder cancer [260]. However, this finding was not confirmed in a subsequent study [1494]. Thrombospondin (TSP-1) is an inhibitor of angiogenesis that is enhanced by interaction with TP53 protein [961]. In one study, a reduced TSP-1 expression was significantly associated with disease recurrence and decreased overall survival [960]. Cyclooxygenase (COX) is an enzyme that converts arachidonic acid into prostaglandin H2. COX-2 is one enzyme subtype that is induced by various stimuli including inflammation and occurs at elevated levels in many tumour types. A high COX-2 expression was related to good prognosis in a series of 172 patients treated by radical cystectomy [2620]. In another study, however, low COX-2 expression was significantly associated with good prognosis in pT1 cancers [1320].
The aim of classification of tumours has always been to define groups with differences in clinical outcomes that are significant enough to be clinically relevant. Also classifications need to be sufficiently reproducible and comprehensive to be uniformly applied by all pathologists and urologists. Further, patients having a benign disease should not be threatened by an unnecessary diagnosis of cancer. And lastly, as molecular pathology research progresses, classification should reflect genetic differences between tumour categories. The presently recommended nomenclature is similar to the WHO-ISUP classification of 1998, but the diagnostic criteria are further defined for practice. The terms non-invasive have been added to low and high grade papillary carcinoma to emphasize biologic differences between these tumours and infiltrating urothelial cancer. The strong points of the current system are:

1. It includes three distinct categories and avoids use of ambiguous grading such as Grade I/II or II/III. The description of the categories has been expanded in the current version of the classification to further improve their recognition.

2. One group (PUNLMP) with particularly good prognosis does not carry the label of ‘cancer’.

3. The group of non-invasive high grade carcinomas is large enough to contain virtually all of those tumours that have similar biological properties (high level of genetic instability) as invasive urothelial carcinomas.

The current classification reflects work in progress. Genetic studies are suggesting two major subtypes of urothelial neoplasms which might have a distinctly different clinical course. As the group of genetically stable tumours appears to include most of the non-invasive low grade carcinomas, it is likely that the group that does not deserve the designation of cancer will increase in the future. If further refinements or modification to this classification are made, they must be on the basis of studies that show superior prediction of prognosis as well as a high degree of reproducibility of morphological or molecular criteria for any newly proposed tumour categories.

The previously used classifications are not recommended for use. It is believed that the consistent use of the current classification will result in the uniform diagnosis of tumours between institutions which will facilitate comparative clinical and pathological studies, incorporation of molecular data and identification of biologically aggressive, genetically instable, non-invasive papillary neoplasms. The potential for this objective to be met also depends on accurate diagnosis and consistent separation of pTa from pT1 tumours in such studies.
Urothelial hyperplasia

Urothelial hyperplasia is defined as markedly thickened mucosa without cytological atypia. It may be seen in the flat mucosa adjacent to low grade papillary urothelial lesions. When seen by itself there is no evidence suggesting that it has any premalignant potential. However, molecular analyses have shown that at least the lesions in bladder cancer patients may be clonally related to the papillary tumours [1930]. Within the spectrum of hyperplasia a papillary architecture may be present; most of these patients have concomitant papillary tumours [2545,2587].

Urothelial dysplasia

Since dysplasia may be mimicked by reactive inflammatory atypia and even by normal urothelium, the spectrum of atypical changes in the urothelium that fall short of carcinoma in situ are described here together.

Definition

Dysplasia (low grade intraurothelial neoplasia) has appreciable cytologic and architectural changes felt to be preneoplastic but which fall short of carcinoma in situ (CIS) [79,84,706].

Epidemiology

Reliable data is unavailable, as most registries record dysplasia along with CIS or consider bladder cancer as a single entity. Since dysplasia is conceptually thought of as precursor lesion of bladder cancer, similar etiopathogenetic factors may apply in dysplasia.

Clinical features

In most cases the diagnosis of bladder cancer precedes dysplasia, and in this setting dysplasia is usually clinically and
cystoscopically silent. Primary (de novo) dysplasia may present with irritative bladder symptoms with or without hematuria [423,1849,2947]. A clinical history of stones, infection, instrumentation or intravesical therapy is often available in reactive cases.

Macroscopy
Lesions may be inapparent or associated with erythema, erosion or, rarely, ulceration.

Histopathology
Normal urothelium
Normal urothelium is urothelium without cytologic atypia and overall maintenance of polarity, or mild architectural alteration (706). It is three to six layers thick, depending on the state of distention, and is composed of basal cells, intermediate cells and superficial cells. Minimal crowding and nuclear overlap without any cytologic abnormality is within the range of normal [79,84,706].

Dysplasia
Lesions show variable often appreciable loss of polarity with nuclear rounding and crowding and cytologic atypia that is not severe enough to merit a diagnosis of CIS. The cells may have increased cytoplasmic eosinophilia and the nuclei have irregular nuclear borders, mildly altered chromatin distribution, inconspicuous nucleoli and rare mitoses. Pleomorphism, prominent nucleoli throughout the urothelium and upper level mitoses argue for a CIS diagnosis [79,84,424,706,1851]. Cytokeratin 20 may be of value in its recognition [261,1023].

Reactive atypia
Reactive atypia occurs in acutely or chronically inflamed urothelium and has nuclear changes clearly ascribable to a reactive/regenerative process. Cells are uniformly enlarged with a single prominent nucleolus and evenly distributed vesicular chromatim. Mitotic activity may be brisk but without atypical forms. Inflammation may be present in the urothelium or lamina propria (79,424).

Urothelial atypia of unknown significance
Atypia of unknown significance is not a diagnostic entity, but a descriptive category for cases with inflammation in which the severity of atypia appears out of proportion to the extent of inflammation such that dysplasia cannot be confidently excluded [424,706]. Alterations vary significantly. This is not meant to be a “waste basket” term but should be used for lesions with atypia that defy categorization but which the observer feels would benefit from clinical follow-up [424,706].

Somatic genetics
Alterations of chromosome 9 and p53 and allelic losses have been demonstrated [534,1031].

Prognostic and predictive factors
Dysplasia is most relevant in non-invasive papillary neoplasms, where its presence indicates urothelial instability and a marker for progression or recurrence (true risk remains to be established) [71,1361,1802,1866,2450]. It is frequently present with invasive cancer, whose attributes determine outcome (1361, 1846). De novo dysplasia progresses to bladder neoplasmia in 5-19% of cases; in most cases, however progressive lesions do not arise from dysplastic regions (79, 423,424,1849,1851,2947).
Urothelial papilloma

Definition
Exophytic urothelial papilloma is composed a delicate fibrovascular core covered by urothelium indistinguishable from that of the normal urothelium.

ICD-O code 8120/0

Epidemiology
The incidence is low, usually 1-4% of bladder tumour materials reported given the above strict definition, but it may be more rare, since in a prospective study of all bladder tumour cases diagnosed during a two year period in Western Sweden no case of urothelial papilloma was identified among 713 patients. The male-to-female ratio is 1.9:1 [432]. Papillomas tend to occur in younger patients, and are seen in children.

Localization
The posterior or lateral walls close to the ureteric orifices and the urethra are the most common locations.

Clinical features
Gross or microscopic hematuria is the main symptom. The endoscopic appearance is essentially identical to that of PUNLMP or Low Grade Papillary Urothelial Carcinoma. Almost all patients have a single tumour. Complete transurethral resection is the treatment of choice. Urothelial papillomas rarely recur (around 8%) [432,1678].

Histopathology
The lesion is characterized by discrete papillary fronds, with occasional branching in some cases, but without fusion. The stroma may show oedema and or scattered inflammatory cells, the epithelium lacks atypia and superficial (umbrella) cells are often prominent. Mitoses are absent to rare and, if present are basal in location and not abnormal. The lesions are often small and occasionally show concomitant inverted growth pattern. Rarely, papilloma may show extensive involvement of the mucosa. This is referred to as diffuse papillomatosis. There has been significant consensus in previous classification systems with regard to the definition and criteria for exophytic urothelial papilloma. The lesions are diploid, mitoses rare and proliferation rates low as deemed by immunohistochemical assessment of e.g. Ki-67 expression [469]. Cytokeratin 20 expression is identical to that in normal urothelium i.e. in the superficial (umbrella) cells only (600,1024). Recent studies claim frequent FGFR3 mutations in urothelial papilloma (75%) [2701] with comparable percentage of mutations in PUNLMP (85%) and Low Grade Papillary Urothelial carcinoma (88%). Alteration of p53 is not seen [469].
Inverted papilloma

Definition
Benign urothelial tumour that has an inverted growth pattern with normal to minimal cytologic atypia of the neoplastic cells.

Epidemiology
The lesion occurs mostly solitary and comprises less than 1% of urothelial neoplasms (1843). The male: female ratio is about 4-5:1. Ages of affected patients range from 10 years (2861) to 94 years (1309) with a peak frequency in the 6th and 7th decades.

Etiology
The etiology of inverted papilloma is unknown. Hyperplasia of Brunn nests and chronic urothelial inflammation have been suggested as possible causes.

Localization
More than 70% of the reported cases were located in the bladder but inverted papillomas can also be found in ureter, renal pelvis, and urethra in order of decreasing frequency. The trigone is the most common location in the urinary bladder (363,596,1037,1049,1190,2416,2494).

Clinical features
Hematuria is the most common symptom. Some cases have produced signs of obstruction because of their location in the low bladder neck or the ureter (503). Dysuria and frequency have been recorded but are uncommon (376).

Macroscopy
Inverted papillomas appear as smooth-surfaced pedunculated or sessile polypoid lesions. Most are smaller than 3 cm in greatest dimension, but rare lesions have grown to as large as 8 cm (363,596,1071,1190,2101).

Histopathology
Inverted papilloma has a relatively smooth surface covered by histologically and cytologically normal urothelium. Randomly scattered endophytic cords of urothelial cells invaginate extensively from the surface urothelium into the subadjacent lamina propria but not into the muscular bladder wall. The base of the lesion is well circumscribed. Anastomosing islands and cords of uniform width distribution appear as if a papillary lesion had invaginated into the lamina propria. In contrast to conventional papillary urothelial neoplasms, the central portions of the cords contain urothelial cells and the periphery contains palisades of basal cells. The relative proportion of the stromal component is mostly minimal but varies from case to case, and within the same lesions. A trabecular and a glandular subtype of inverted papilloma have been described (1409). The trabecular type is composed of interanastomosing sheets of urothelium sometimes including cystic areas. The glandular subtype contains urothelium with pseudoglandular or glandular differentiation. Foci of mostly non-keratinizing squamous metaplasia are often seen in inverted papillomas. Neuroendocrine differentiation has also been reported (2534). Urothelial cells have predominantly benign cytological features but focal minor cytologic atypia is often seen (363,1409,1843). Mitotic figures are rare or absent (363,1409).

It is important to not extend the diagnosis to other polypoid lesions with predominantly subsurface growth pattern such as florid proliferation of Brunn nests or areas of inverted growth in non-invasive papillary tumours.

Fig. 2.34 Noninvasive urothelial neoplasm. A, B Inverted papilloma. C Most urothelial cells in this example of inverted papilloma are immunohistochemically reactive with antibodies anti-cytokeratin 7.
Somatic genetics
Ultrastructure, antigenic composition, and DNA-content of inverted papilloma cells have been non-contributory to the diagnosis in the few evaluated cases [68,447,1190,1406].

Prognosis
If the diagnosis of inverted papilloma is strictly confined to the criteria described above, these tumours are benign. Recurrent lesions have been observed in less than 1% of the reported cases [376] and progression from pure inverted papilloma to carcinoma is extremely rare. An initial diagnosis of inverted papilloma should be challenged if progression is observed as many recurring or progressing cases have exophytic papillary structures in their initial biopsy [78].

Papillary urothelial neoplasm of low malignant potential

Definition
Papillary Urothelial Neoplasm of Low Malignant Potential (PUNLMP) is a papillary urothelial tumour which resembles the exophytic urothelial papilloma, but shows increased cellular proliferation exceeding the thickness of normal urothelium.

ICD-O code 8130/1

Epidemiology
The incidence is three cases per 100,000 individuals per year. The male to female ratio is 5:1 and the mean age at diagnosis (+/- standard deviation) is 64.6 years +/-13.9 years (range 29-94) [1107]. The latter is virtually identical to that of 112 patients treated at the Mayo Clinic [432].

Localization
The lateral and posterior walls close to the ureteric orifices are the preferred sites for these tumours.

Clinical features
Most patients present with gross or microscopic hematuria. Urine cytology is negative in most cases. Cystoscopy reveals, in general, a 1-2 cm regular tumour with a appearance reminiscent of “seaweed in the ocean”. Complete transurethral resection is the treatment of choice.

Histopathology
The papillae of PUNLMP are discrete, slender and non fused and are lined by multilayered urothelium with minimal to absent cytologic atypia. The cell density appears to be increased compare to normal. The polarity is preserved and there is an impression of predominant order with absent to minimal variation in architectural and nuclear features. The nuclei are slightly enlarged compare to normal. The basal layers show palisading and the umbrella cell layer is often preserved. Mitoses are rare and have a basal location. These architectural and cytological features should be evaluated in well oriented, non tangential cut areas of the neoplasm. The tumours are predominantly diploid.

Prognosis
The prognosis for patients with PUNLMP is excellent. Recurrences occur, but at a significantly lower frequency than in non-invasive papillary carcinomas [1610]. Rarely, these patients may present with another tumour of higher grade and/or stage, usually years after the initial diagnosis. In a series of 95 cases, 35% had recurrence but no tumour progressed. If the patients were tumour free at the first follow-up cystoscopy, 68% remained tumour free during a follow-up period of at least 5 years [1104,1110]. In another study, 47% of the patients developed local recurrence but none of the 19 PUNLMP patients progressed [2071]. In contrast, in a retrospective study of 112 patients with long term follow up, four patients progressed in stage, two to
muscle invasive disease, but there was only a 25% recurrence rate (432).

**Non-invasive papillary urothelial carcinoma, low grade**

**Definition**
A neoplasm of urothelium lining papillary fronds which shows an orderly appearance, but easily recognizable variations in architecture and cytologic features.

**ICD-O code** 8130/21

**Epidemiology**
The incidence is five cases per 100,000 individuals per year. The male-to-female ratio is 2.9:1. The mean age (+/- standard deviation) is 69.2 years, +/- 11.7 (range 28-90 years) (1107).

**Localization**
The posterior or lateral walls close to the ureteric orifices is the site of approximately 70% of the cases.

**Clinical symptoms**
Gross or microscopic hematuria is the main symptom. The endoscopic appearance is similar to that of PUNLMP. In 78% of the cases the patients have a single tumour and in 22% there are two or more tumours (1108).

**Histopathology**
The tumour is characterized by slender, papillary stalks which show frequent branching and minimal fusion. It shows an orderly appearance with easily recognizable variations in architectural and cytologic features even at scanning power. In contrast to PUNLMP, it is easy to recognize variations in nuclear polarity, size, shape and chromatin pattern. The nuclei are uniformly enlarged with mild differences in shape, contour and chromatin distribution. Nucleoli may be present but inconspicuous. Mitoses are infrequent and may occur at any level but are more frequent basally. The papillary fronds should be evaluated where sectioned lengthwise through the core or perpendicular to the long axis of the papillary frond. If not, there may be a false impression of increased cellularity, loss of polarity and increased mitotic activity.

Fig. 2.37 Non-invasive urothelial neoplasm. A,B Papillary urothelial neoplasm of low malignant potential (PUNLMP).

Fig. 2.38 Non-invasive urothelial neoplasm. A,B Non-invasive low grade urothelial carcinoma.

Fig. 2.39 Non-invasive low grade papillary urothelial cancer. FISH analysis shows monosomy of Chromosome 9 (red dot).
Non-invasive papillary urothelial carcinoma, high grade

**Definition**
A neoplasm of urothelium lining papillary fronds which shows a predominant pattern of disorder with moderate-to-marked architectural and cytologic atypia.

**ICD-O code** 8130/23

**Clinical symptoms**
Gross or microscopic hematuria is the main symptom. The endoscopic appearance varies from papillary to nodular/solid sessile lesions. Patients may have single or multiple tumours.

**Histopathology**
The tumour is characterized by a papillary architecture in which the papillae are frequently fused and branching, although some may be delicate. It shows a predominant pattern of disorder with easily recognizable variations in architecture.

In spite of the overall orderly appearance, there are tumours that show focal high grade areas and in these cases the tumour should be classified as a high grade tumour. Expression of cytokeratin 20, CD44, p53 and p63 immunostaining is intermediate between that of PUNLMP and non-invasive high grade papillary urothelial carcinoma (600,2678). The tumours are usually diploid (2071).

**Prognosis**
Progression to invasion and cancer death occurs in less than 5% of cases. In contrast, recurrence is common and occurs in 48-71% of the patients (69, 1104,1110).

![Flow chart of the differential diagnosis of non-invasive papillary urothelial tumours.](image)

**Fig. 2.40** Flow chart of the differential diagnosis of non-invasive papillary urothelial tumours.

**Fig. 2.41** Non-invasive papillary urothelial carcinoma, high grade. **A** The papillary fronds are partially fused and lined by markedly atypical and pleomorphic urothelial cells, some of which have exfoliated. **B** The architecture is disordered and there is marked nuclear pleomorphism and hyperchromasia. Mitotic figures are readily visible away from the basement membrane. **C** The nuclei have open chromatin, irregular nuclear contours and variably prominent nucleoli. There is total lack of polarization and maturation.
Tectural and cytologic features even at scanning power. In contrast to non-invasive low grade papillary urothelial carcinoma, it is easy to recognize more marked variations in nuclear polarity, size, shape and chromatin pattern. The nuclei often show pleomorphism with moderate-to-marked variation in size and irregular chromatin distribution. Nucleoli are prominent. Mitoses are frequent, may be atypical, and occur at any level, including the surface. The thickness of the urothelium may vary considerably and often with cell dyscohesion. Within this category of these tumours there is a spectrum of atypia, the highest of which show marked and diffuse nuclear pleomorphism. Pathologists have the option of recording the presence or absence of diffuse anaplasia in a comment. The papillary fronds should be evaluated where sectioned lengthwise through the core or perpendicular to the long axis of the papillary frond. Due to the likelihood of associated invasion, including that of papillary cores, these features should be closely looked for.

Detection of cytokeratin 20, p53 and p63 is more frequent than in low grade tumours (600,2678). The tumours are usually aneuploid (2071).
Urothelial carcinoma in situ

I.A. Sesterhenn

Definition
A non-papillary, i.e. flat, lesion in which the surface epithelium contains cells that are cytologically malignant.

ICD-O code 8120/2

Synonym
High grade intraurothelial neoplasia.

Incidence
De novo (primary) carcinoma in situ accounts for less than 1-3% of urothelial neoplasms, but is seen in 45-65% of invasive urothelial carcinoma. It is present in 7-15% of papillary neoplasms [744,1362,1850,2315,2836].

Site of involvement
Urothelial carcinoma in situ is most commonly seen in the urinary bladder. In 6-60%, the distal ureters are involved. Involvement of the prostatic urethra has been reported in 20-67% and in the prostate, involving ducts and acini, in up to 40%. It may be seen in the renal pelvis and proximal ureters [744,798,921,1362,1596,2187,2319,2679].

Clinical features
CIS patients are usually in the 5th to 6th decade of life. They may be asymptomatic or symptomatic with dysuria, frequency, urgency or even hematuria. In patients with associated urothelial carcinoma, the symptoms are usually those of the associated carcinoma.

Macroscopy
The mucosa may be unremarkable or erythematous and oedematous. Mucosal erosion may be present.

Histopathology
Urothelial carcinoma in situ shows nuclear anaplasia identical to high grade urothelial carcinoma. The enlarged nuclei are frequently pleomorphic, hyperchromatic, and have a coarse or condensed chromatin distribution; they may show large nucleoli. Mitoses including atypical ones are common and can extend into the upper cell layers. The cytoplasm is often eosinophilic or amphophilic. There is loss of cell polarity with irregular nuclear crowding [425,706,743,1547,1798,1844,1845,1982]. The neoplastic change may or may not involve the entire thickness of the epithelial layer and umbrella cells may be present. It may be seen at the basal layer only or may overlay benign appearing epithelium. Individual cells or clones of neoplastic cells may be seen scattered amidst apparently normal urothelial cells and this is referred to as pagetoid spread [425,1547,1552,1678,1982]. Loss of intercellular cohesion may result in a denuded surface ("denuding cystitis") [688] or in residual individual neoplastic cells.
cells attached to the surface referred to as "clinging" CIS. In such cases cytology is very helpful. Von Brunn nests and cystitis cystica may be completely or partially replaced by the cytologically malignant cells. CIS may consist of predominantly small cells referred to as small cell variant or of rather large cells. CIS commonly is multifocal and may be diffuse. It can involve several sites in the urinary tract synchronously or metachronously. The degree of cellular atypia may vary from site to site. The lamina propria usually shows an inflammatory infiltrate, some degree of oedema and vascular congestion.

Immunoprofile
Markers, which are abnormally expressed in invasive and papillary urothelial neoplasm have also been evaluated in CIS [494,964]. Cytokeratin 20 is abnormally expressed in CIS [1023]. Abnormal expression of p53 and RB protein may correlate with progression of CIS [498,725,2294,2364,2457]. The nuclear matrix protein NMP22 is present in CIS [2484].

Ploidy
The DNA analysis shows an aneuploid cell population, in some patients several aneuploid cell populations are present in the same lesion [977,1918,2060,2641].

Prognosis
Data suggest that de novo (primary) CIS is less likely to progress to invasive disease than secondary CIS [1918,2115,2237,2803]. Patients with CIS and concomitant invasive tumours die in 45-65% of cases compared to 7-15% of patients with CIS and concomitant non-invasive papillary tumour [1846]. CIS with multiple aneuploid cell lines appears to be at high risk of progression [1918]. Extensive lesions associated with marked symptoms have a guarded prognosis.

Genetics and predictive factors of non-invasive urothelial neoplasias

Genetics of urinary bladder cancer development and progression
The genetic studies to date have used tumours classified according to the 1973 WHO Tumours Classification; studies are underway to link available genetic information to the current classification. Urinary bladder cancer has earlier been categorized into "superficial" (pTa, pT1, CIS) and "invasive" (pT2-4) cancer depending on whether or not tumour infiltration extended to the muscular bladder wall [2133]. The available genetic data now suggest another subdivision of urinary bladder neoplasia. Two genetic subtypes with marked difference in their degree of genetic instability correspond to morphologically defined entities. The genetically stable category includes low grade non-invasive papillary tumours (pTa). The genetically unstable category contains high grade (including pTa G3 and CIS) and invasively growing carcinomas (stage pT1-4). Non-invasive low grade papillary bladder neoplasms (pTa, G1-2) have only few genomic alterations and are therefore viewed as "genetically stable" [2189,2418,2552,2934]. Losses of chromosome 9, often involving the entire chromosome, and mutations of FGFR3 are the most frequently known genetic alterations in these tumours. Gene amplifications and TP53 mutations are rare [818,1748,2066,2190,2421,2422]. DNA aneuploidy occurs in less than 50% [2304,2599,2931]. Invasively growing and high grade neoplasias are markedly different from non-invasive papillary low grade tumours. They appear to be genetically unstable and have many different chromosomal...
aberrations, often including high level amplifications and p53 mutations (496,1415,1920,2468). DNA aneuploidy is seen in >90% (2304,2931). Genetic differences between minimally invasive (pT1) and extensively invasive (pT2-4) carcinomas are only minimal (2188, 2419). Some reports have suggested a possible role of 5p+, 5q-, and 6q- for further progression from pT1 to pT2-4 cancers (263,1101,2191,2316). Only few studies have investigated non-invasive high grade precursor lesions (pTaG3, CIS) (1031,2241). These data suggest a strong similarity between these tumours and invasively growing cancers, which is consistent with their assumed role as precursors of invasive bladder cancer. The high number of individual genetic alterations that are much more frequent in high grade or invasive tumours than in pTaG1-G2 neoplasias makes it unlikely that a relevant fraction of invasive cancers derives from non-invasive papillary low grade tumours. This is also consistent with the clinical observation that the vast majority of invasive bladder cancer was not preceded by a pTa G1/G2 tumour (1363). Combining pT1 cancers and pTa tumours into one group as "superficial bladder cancer" should be rigorously avoided (2188,2419). Precursor lesions of either invasive or non-invasive urothelial tumours include hyperplasia since significant chromosomal aberrations can be found in these lesions, also in absence of dysplasia (1029). Chromosomal aberrations can also be seen in histologically 'normal appearing urothelium' in bladders from cancer patients. This suggests that genetic analysis may be superior to histology for diagnosis of early neoplasia (2492). Only few studies have analyzed genetic changes in dysplasia (1031, 1488,2397,2492). They showed, that alterations that are typical for CIS can be also be found in some dysplasias suggesting that at least a fraction of them can be considered CIS precursors.

Multifocal bladder neoplasms

Neoplasias of the urothelium are typically not limited to one single tumour. Multifocality, frequent recurrence, and presence of barely visible flat accompanying lesions such as hyperplasia or dysplasia are characteristic for these tumours. Morphological, cytogenetic and immunohistochemical mapping studies of cystectomy specimens have demonstrated areas of abnormal cells adjacent to grossly visible tumours (1164,1362) (cytogenetic). The majority (80-90%) of multicentric bladder neoplasias are of monoclonal origin {437,541,733,986, 1030,1492, 1564,1751,2405,2420,2552,2553,2859}. It is assumed that neoplastic cells that have originated in one area later spread out to other regions either by active migration through the urothelium or through the urine by desquamation and reimplantation (992). However, there are also reports of polyclonality, mainly in early stage tumours or in premalignant lesions (915,993,1030,1751, 2059,2467,2883). These observations have given rise to the 'field defect' hypothesis suggesting that environmental mutagens may cause fields of genetically altered cells that become the source of polyclonal multifocal tumours (1362). It appears possible that selection and overgrowth of the most rapidly growing clone from an initially polyclonal neoplasia might lead to pseudoclonality in some cases of multiple bladder cancer. Presence or absence of monoclonality may have an impact on the clinical treatment modalities.

Chromosomal abnormalities

Non-invasive papillary low grade neoplasias (pTa, G1-2) have only few cytogenetic changes suggesting that these tumours are genetically stable neoplasias (2189,2418,2552,2934). Total or partial losses of chromosome 9 is by far the most frequent cytogenetic alteration in these tumours, occurring in about 50% of bladder cancers of all grades and stages (2189,2307,2418). Chromosome 9 loss can also be found in hyperplasia and even in morphologically normal appearing urothelium (1029,2492). They showed, that the losses of the Y chromosome represent the next most frequent cytogenetic alteration in low grade tumours (2310,2934). The biologic significance of this alteration is unclear since Y losses can also be found in normal urothelium from patients without a bladder cancer history (2310). High grade non-invasive precursor lesions (pTaG3, CIS) are very different from low grade neoplasias. Cytogenetically, they resemble invasively growing tumours and have many different genomic alterations (2241,2656, 2934). A CGH study showed predominant deletions at 2q, 5q, 10q, and 18q as well as gains at 5p and 20q in 18 pTaG3 tumours (2934). A high frequency of LOH at different loci was also observed in 31 CIS samples. Predominant alterations were LOH at 3p, 4q, 5q, 8p, 9q, 11p, 13q, 14q, 17p and 18q in this study (2241). Alterations in the cellular DNA content occur frequently in bladder cancer (1120,2059,2304). Aneuploidy is strongly associated to stage and grade, and differences are most striking between pTa and pT1 tumours (2304). Aneuploidy detection (e.g. by FISH or by cytometry) may be a suitable tool for the early detection of bladder cancer and recurrences. It has been shown that a panel of 4 FISH probes is sufficient to detect chromosomal alterations in bladder tumours and tumour cells in voided urines (334,2304, 2492).

Chromosome 9

The similar frequency of chromosome 9 losses in non-invasive papillary low grade tumours and in high grade invasive cancers triggered extensive research to find the suggested one or several tumour suppressor genes on chromosome 9 that appear to play an important role in bladder cancer initiation (361,985,2648). Mapping studies using microsatellite analysis identified multiple common regions of loss of heterozygosity (LOH) (361,982,1291,2423). Two of them have been identified at 9p21, the loci of the cell cycle control genes CDKN2A (p16/p14ARF) and CDKN2B (p15) (1291). Another three putative suppressor gene loci have been mapped to 9q13-q31, 9q32-q33 and 9q34, containing the PTCH, DBCCR1 and TSC1 genes (988). Because homozygous deletions are slightly more frequent for CDKN2A than for CDKN2B it has been postulated that p16/p14ARF might be the primary target of 9p21 deletions (1975). On 9q, the putative cell cycle regulator DBCCR1 (deleted in bladder cancer chromosome region candidate 1), which might be involved in cell cycle regulation (984, 1988), seems to be a promising candidate tumour suppressor. Loss of DBCCR1 expression has been found in 50% of bladder tumours (984), and FISH analysis revealed deletions of 9q33 in 73% of samples (2476). Mutations of DBCCR1 have not been reported yet. Although hemizygous deletions have been seen in rare cases it is believed that promoter hypermethylation and homozygous deletions are the main mechanisms.
for DBCCR1 silencing (984,2476). The role of the sonic hedgehog receptor PTCH and the tuberous sclerosis gene TSC1 in bladder cancer is only poorly investigated to date.

**FGF receptor 3 (FGFR3)**

Mutations of the gene, located at chromosome 4p16.3, have only recently been identified as a molecular alteration that is characteristic for pTa tumours. In the largest study reported to date, 74% of pTa tumours had FGFR3 mutation as compared to 16% of T2-4 tumours (243). All mutations described are missense mutations located in exons 7, 10 or 15 that have been previously described as germline mutations in skeletal dysplasia syndromes (369,2403). These mutations are predicted to cause constitutive activation of the receptor. In one study, mutations have been linked to a lower risk of recurrence indicating that this genetic event may identify a group of patients with favourable disease course (2700). In a recent study (2701), comparable FGFR3 mutation frequencies were reported in 9 of 12 papillomas (75%), 53 of 62 tumours of low malignant potential (85%), and 15 of 17 low grade papillary carcinomas (88%). These data support the idea that these categories represent variations of one tumour entity (non-invasive low grade papillary tumours; genetically stable).

**TP53 and RB**

Alterations of TP53 (818,1748,2066), and the retinoblastoma gene (RB) (1749, 2112) occur in a fraction of non-invasive papillary low grade tumours that is much smaller than in invasive cancer.

**HER2 & EGFR**

Overexpression of HER2 or EGFR have been described in a variable fraction of pTaG1/G2 tumours depending on the analytical methodology (914,1757,1758). Few studies have examined gene alterations in CIS or pTaG3 tumours; they showed comparable frequencies of p53 alterations (50-70%) [1031,1119], HER2 overexpression (50-75%) [489,2761], or EGFR overexpression (45-75%) [373, 2761], and loss of p21 (50-70%) [472, 2761] or p27 (50%) [797] as described in invasive cancers. Increased expression of Ras protein has been described in CIS and high grade tumours but not in hyperplasia or low grade tumours in an early study (2736). However, the role of RAS especially in non-invasive bladder cancer needs further clarification (2395).

### Prognosis and predictive factors

#### Clinical factors

There are no specific urinary symptoms of non-invasive bladder tumours. Microscopic or gross hematuria are the most common findings (1719). Irritative bladder symptoms such as dysuria, urgency and frequency occur if the tumour is localized in the trigone, in case of large tumour volume due to reduction of bladder capacity, or in case of carcinoma in situ.

At the time of first diagnosis approximately 70% of the tumours are non-invasive and of these only 5 to 10% will progress to infiltrating tumours (544). However, half of all the tumours will recur at some time. Large tumours, multifocal tumours and those with diffuse appearance have a higher risk of recurrence (773). In case of recurrent tumour, the probability of future recurrences, increase to approximately 80%. Short disease-free interval is also an indication for future recurrence. In case of carcinoma in situ, irritative symptoms and extensive disease are associated with poor prognosis (71).

As discrimination between non-invasive and invasive tumours is not reliably possible on cystoscopy alone, complete transurethral resection of any visible lesion of the bladder including deep muscle layers is usually performed.

Regular cystoscopic follow-up is recommended at intervals for all patients with non-invasive tumours to detect recurrent tumour at an early stage. The risk of recurrence decreases with each normal cystoscopy and is less than 10% at 5 years and extremely low at 10 years if all interval cystoscopies had been normal.

#### Morphological factors

Histologic grade is a powerful prognostic factor for recurrence and progression in non-invasive urothelial tumours (706,1440,1610). Urothelial papilloma has the lowest risk for either recurrence or progression (426,654,1678), while PUNLMP has a higher risk for recurrence (up to 35%) and a very low risk for progression in stage (432,1104,1107, 1247,1460). Patients with papilloma and PUNLMP have essentially a normal age-related life expectancy. Non-invasive low

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(C) = CGH; (K) = karyotyping/classical cytogenetics (average of 32 cases from references [13,15,123,149,180,186,188,190,192,242,2639,2702,2766]; (L) = LOH; (F) = FISH (FISH analyses of ICGNU have been included because of the lack of CGH data in this tumour type).
grade carcinomas recur frequently (up to 70%), but only up to 12% of patients progress in stage [433,600,1104, 1107,1460]. The prognosis for non-invasive high grade carcinomas is strikingly different. Tumours frequently progress in stage, and death due to disease can be as high as 65% (1247,1461).

Patients with multifocal tumours in the bladder or involving other regions of the urothelial tract (ureter, urethra, renal pelvis) are at increased risk for recurrence, progression or death due to disease [531,1314,1579,2019]. The presence of dysplasia and CIS in the nonpapillary urothelium is associated with increased risk for progression in stage and death due to disease [71,425, 726,1981,2450]. CIS is a stronger adverse factor [425,726,1981].

Large tumours (>5 cm) are at an increased risk for recurrence and progression [1072].

**Genetic factors**

Hundreds of studies have analyzed the prognostic significance of molecular features in non-invasive urinary bladder cancer [1340,2496,2725,2827]. Overall, there is no thoroughly evaluated molecular marker that has sufficient predictive power to be of clinical value in these tumours. There is circumstantial evidence that in some studies the substantial biological differences between non-invasive (pTa) and invasively growing (pT1) neoplasias were not taken into account [2189,2306,2418,2242]. Since the risk of progression is much higher in pT1 than in pTa tumours, and the frequency of most molecular changes is highly different between pTa and pT1 tumours, it must be assumed that interobserver variability in the distinction of pTa and pT1 tumours may markedly influence the results [19,2633,2835]. A systematic review of large series of pT1 tumours resulted in a downstaging to stage pTa in 25-34% of tumours [19,2633,2835]. Accordingly, the percentage of pT1 cancers varies between 20% and 70% in consecutive series of “superficial bladder cancers” [249,2065, 2066,2322]. A too large fraction of overstaged “false” pT1 tumours can even suggest independent prognostic impact of molecular features in combined pTa/pT1 studies.

**Risk of recurrence**

Non-invasive urothelial neoplasia often involves invisible flat neoplastic lesions in addition to a visible papillary tumour [285,1362]. After complete resection of a tumour, the risk of recurrence is determined by the amount and biologic properties of neoplastic cells remaining in the bladder. Multicentric neoplastic lesions in the bladder are clonally related in about 80-90% of cases (992). Only in these cases, the molecular characteristics of the removed tumour may be representative of the “entire” disease. The best candidates for predicting early recurrence include molecular changes that are related to an increased tumour cell proliferation or an improved potential for multicentric tumour extension. Indeed, several studies showed that rapid tumour cell proliferation as measured by flow cytometry, mitotic index, PCNA labeling, or Ki67 labeling index predicts an increased risk of or recurrence in these tumours [573,1452,1512,1518,2942]. Cytokeratin 20 expression and FGFR mutations are examples of markers that may be representative for a clinically distinct tumour subtype without having a direct role for the development of early recurrence. Cytokeratin 20 is normally expressed in the superficial and upper intermediate urothelial cells. In a study of 51 non-invasive papillary tumours, none of 10 tumours with a normal cytokeratin 20 staining pattern recurred [1024]. Mutations of the FGF receptor 3 (FGFR3) have recently been identified to occur in more than two thirds of non-invasive low grade urothelial carcinoma [243]. Early studies suggest that mutations are linked to a decreased risk of recurrence [2700]. Other molecular features that were proposed to predict tumour recurrence in non-invasive papillary low grade tumours include overexpression of proline-directed protein kinase F (1132), p14ARF promoter hypermethylation [632], clusterin overexpression [1746], expression of the imprinted H19 gene [115], and reduced expression of E-cadherin [1511].

Early tumour recurrence could also be predicted by the analysis of urine cells after surgical removal of all visible tumours. Studies using fluorescence in situ hybridization (FISH) have indeed shown a strong prognostic significance of genetically abnormal cells for early recurrence in cystoscopically and cytologically normal bladders [801,1179, 2298].

**Risk of progression**

Data on the prognostic importance of genetic changes for progression of non-invasive low grade neoplasias are largely missing because of the rarity of progression in these patients. In theory, molecular changes that decrease genetic stability are expected to herald poor prognosis in these patients, because an acquisition of multiple additional molecular changes may be required to transform non-invasive low grade neoplasia to invasive cancer. In fact, p53 alterations, known to decrease genomic stability, have been suggested as a prognostic marker in pTa tumours [2296].

Molecular parameters that were suggested to herald a particularly high risk of progression include p53 accumulation [2294], reduced thrombospondin expression [898], loss of p63 expression [2678], loss of E-cadherin expression [1210], abnormal expression of pRb [963], LOH at chromosome 16p13 [2879], as well as alterations of chromosomes 3p, 4p, 5p, 5q, 6q, 10q, and 18q [2191].
Squamous cell carcinoma

**Definition**
A malignant neoplasm derived from the urothelium showing histologically pure squamous cell phenotype.

**ICD-O code** 8070/3

**Epidemiology**
The most common histological type of bladder cancer is urothelial carcinoma, which comprises 90-95% of bladder cancers in Western countries [2016]. Squamous cell carcinoma (SCC) of the bladder is much less frequent. Worldwide, it constitutes about 1.3% of bladder tumours in males, and 3.4% in females. In the United States, the differences in histology by race are small, with whites having 94.5% urothelial and 1.3% squamous cell carcinomas (SCCs), while the proportions are 87.8% and 3.2%, respectively, in Blacks. In Africa, the majority of bladder cancers in Algeria and Tunisia (high incidence countries) are urothelial carcinomas, with SCCs comprising less than 5%. In some West African countries (Mali, Niger), and in east and south-east Africa (Zimbabwe, Malawi, Tanzania), SCC predominates, as it does in Egypt. In South Africa, there are marked differences in histology between Blacks (36% SCC, 41% urothelial) and Whites (2% SCC, 94% urothelial) [2013]. Similar findings with respect to black-white differences in proportions of the different histological types of bladder cancer have been reported from clinical series, for example in the Durban hospitals (955). These observations (as well as clinical features such as sex ratio, mean age at diagnosis and stage) relate to the prevalence of infection with *Schistosoma haematobium*.

**Etiology**

**Tobacco smoking**
Tobacco smoking is the major established risk factor for bladder cancer. The risk of bladder cancer in smokers is 2-6 fold that of non-smokers (1158). The risk increases with increasing duration of smoking, as well as with increasing intensity of smoking (313). Tobacco smoking is also an important risk factor for SCC of the bladder. It has been estimated that the relative risk for current smokers is about 5-fold of that in non-smokers (791). The risk increases with the increasing lifetime consumption, and for those with the highest consumption (more than 40 pack-years) is about 11 (791), as well as with increasing intensity of smoking (1271).

**Occupational exposures**
As described earlier, bladder cancer risk is increased in various occupational groups, but the effect of occupational exposures has not been quantified for different histological types.

**Schistosomiasis**
Schistosomes are trematode worms that live in the bloodstream of humans and animals. Three species (*Schistosoma haematobium*, *S. mansoni* and *S. japonicum*) account for the majority of human infections. The evidence linking infection with *Schistosoma haematobium* with bladder cancer has been extensively reviewed (419,1152,1791)). There are essentially three lines of evidence: Clinical observations that the two diseases appear to frequently co-exist in the same individual, and that the bladder cancers tend to be of squamous cell origin, rather than urothelial carcinomas. Descriptive studies showing a correlation between the two diseases in different populations. Case-control studies, comparing infection with *S. haematobium* in bladder cancer cases and control subjects. Several studies investigated this relationship, taking as a measure of infection the presence of *S. haematobium* eggs in a urine sample, presence of calcified eggs identified by X-ray or information from a questionnaire (199,687,846,1859,2739). The
estimated relative risk varied from 2 to 15 compared with non-infected subjects.

**Pathogenesis**
Numerous explanations have been offered for the proposed association between schistosomiasis and human cancers:
- **Chronic irritation and inflammation** with increased cell turnover provide opportunities for mutagenic events, genotoxic effects and activation of carcinogens through several mechanisms, including the production of nitric oxide by inflammatory cells (activated macrophages and neutrophils) \(^{(2240,2242)}\).
- **Altered metabolism of mutagens** may be responsible for genotoxic effects \(^{(851,852,853)}\). Quantitatively altered tryptophan metabolism in *S. haematobium*-infected patients results in higher concentrations of certain metabolites (e.g. indican, anthranilic acid glucuronide, 3-hydroxyanthranilic acid, L-kynurenine, 3-hydroxy-L-kynurenine and acetyl-L-kynurenine) in pooled urine \(^{(11,12,806)}\). Some of these metabolites have been reported to be carcinogenic to the urinary bladder \(^{(332)}\).
- **Secondary bacterial infection** of *Schistosoma*-infected bladders is a well documented event \(^{(678,1091,1093,1449,1468)}\) and may play an intermediary role in the genesis of squamous-cell carcinoma via a variety of metabolic effects. Nitrate, nitrite and N-nitroso compounds are detected in the urine of *S. haematobium*-infected patients \(^{(14,1090,1091,1092,2642,2643)}\). Nitrosamines are formed by nitrosation of secondary amines with nitrates by bacterial catalysis (or via urinary phenol catalysis); they may be carcinogenic to bladder mucosa.
- **Elevated \(\beta\)-glucuronidase levels** in schistosome-infected subjects could increase the release of carcinogenic metabolites from their glucuronides. No data are available at present to confirm this association, although schistosome-infected humans are known to have elevated \(\beta\)-glucuronidase activity in urine \(^{(9,10,15,679,683,805,1916)}\), for reasons that are unknown.
- **Genetic damage** in the form of slightly increased sister chromatid exchange and micronucleus frequencies were seen in peripheral blood lymphocytes harvested from schistosomiasis patients \(^{(104,2399)}\), and micronuclei were more frequent in urothelial cells from chronic schistosomiasis patients than in controls \(^{(2239)}\).

**Macroscopy**
Most squamous cell carcinomas are bulky, polypoid, solid, necrotic masses, often filling the bladder lumen \(^{(2297)}\), although some are predominantly flat and irregularly bordered \(^{(1884)}\) or ulcerated and infiltrating \(^{(1233)}\). The presence of necrotic material and keratin debris on the surface is relatively constant.

**Histopathology**
The diagnosis of squamous cell carcinoma is restricted to pure tumours \(^{(232,745,2297)}\). If an identifiable urothelial element including urothelial carcinoma in situ is found, the tumour should be classified as urothelial carcinoma with squamous differentiation \(^{(2276)}\). The presence of keratinizing squamous metaplasia in the adjacent flat epithelium, especially if associated with dysplasia, supports a diagnosis of squamous cell carcinoma. Squamous metaplasia is identifiable in the adjacent epithelium in 17-60% of cases from Europe and North America \(^{(232)}\). The invasive tumours may be well differ-
entiated with well defined islands of squamous cells with keratinization, prominent intercellular bridges, and minimal nuclear pleomorphism. They may also be poorly differentiated, with marked nuclear pleomorphism and only focal evidence of squamous differentiation. A basaloid pattern has been reported [2682].

**Somatic genetics**

Genetic analyses of squamous cell carcinomas (SQCC) of the urinary bladder focused on Schistosoma associated tumors. Cytogenetic and classic molecular analyses showed overrepresentation of chromosomal material predominantly at 5p, 6p, 7p, 8q, 11q, 17q, and 20q, while deletions were most frequent at 3p, 4q, 5q, 8p, 13q, 17p, and 18q [74,681, 735,912,1858,2118,2380]. Several studies suggested differences in the frequency and type of p53 alterations between urothelial carcinoma and Schistosoma associated SQCC [987,2141,2784]. However, the rate of p53 positive tumours ranged between 30-90% in all studies (average 40%; n=135) [987, 2141,2784], which is not significantly different from the findings in urothelial cancer. In one study, TP53 mutations in Schistosoma associated SQCC included more base transitions at CpG dinucleotides than seen in urothelial carcinomas [2784]. Other molecular alterations known to occur in urothelial carcinomas such as HRAS mutations (6-84%) [2117,2127], EGFR overexpression (30-70%) [337,1921], and HER2 expression (10-50%), [225,489,836,914,1509,1527, 1708,1974,2152,2309] were also found at comparable frequencies in Schistosoma associated SQCC [2141]. Only few non Schistosoma associated “sporadic” SQCC have been molecularly analyzed.

**Prognosis and predictive factors**

**Clinical criteria**

Patient-related factors, e.g. sex and age are not prognostic in squamous cell bladder cancer [692]. In contrast, T-stage, lymph node involvement and tumour grade have been shown to be of independent prognostic value [2118, 2373]. Patients undergoing radical surgery appear to have an improved survival as compared to radiation therapy and/or chemotherapy, while neoadjuvant radiation improves the outcome in locally advance tumours [866].

**Morphologic factors**

Pathologic stage is the most important prognostic parameter for squamous cell carcinoma [692]. The tumours are staged using the AJCC/TNM system as for urothelial carcinoma [944]. In a series of 154 patients, overall 5-year survival was 56%; for those patients with organ-confined tumour (pT1,2) it was 67% and for non organ-confined (pT3,4) it was only 19% [692]. There are no uniformly accepted criteria for grading of squamous cell carcinoma. Squamous cell carcinoma of the bladder has been graded according to the amount of keratinization and the degree of nuclear pleomorphism [745,1884]. Several studies have demonstrated...
grading to be a significant morphologic parameter (692,745,1884). In one series, 5-year survivals for Grade 1, 2 and 3 squamous cell carcinoma was 62%, 52% and 35%, respectively (692). This has not been a uniform finding however (2263).

One recent study analyzing 154 patients that underwent cystectomy suggested that a higher number of newly formed blood vessels predicts unfavourable disease outcome (692).

**Genetic predictive factors**

Nothing is known on the impact of genetic changes on the prognosis of SQCC of the urinary bladder.

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**Verrucous squamous cell carcinoma**

**ICD-O code** 8051/3

Verrucous carcinoma is an uncommon variant of squamous cell carcinoma that occurs almost exclusively in patients with schistosomiasis, accounting for 3% to 4.6% of bladder cancers in such a setting (680,682). Isolated cases of verrucous carcinoma of the urinary bladder have been described in the literature from non-endemic areas (691,1102,2772,2851). This cancer appears as an exophytic, papillary, or “warty” mass with epithelial acanthosis and papillomatosis, minimal nuclear and architectural atypia and rounded, pushing, deep borders. Cases having typical verrucous carcinoma with an infiltrative component are described and should not be included in the verrucous carcinoma category (1603). In other organs, verrucous carcinoma has a good prognosis, but results in the bladder are limited. Cases of classic verrucous carcinoma are associated with minimal risk of progression whether associated with schistosomiasis or without (680,691,1102,2772,2851). Tumours developing in patients with longstanding anogenital condyloma acuminata and condyloma acuminatum of the urinary bladder are reported suggesting a possible link to HPV infection (186,2772).

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**Squamous cell papilloma**

**ICD-O code** 8052/0

Squamous cell papilloma of the urinary bladder is a very rare benign, proliferative squamous lesion. It occurs in elderly women without specific clinical symptoms (428). In most cases the cystoscopy shows a solitary papillary lesion (428). It is not associated with human papillomavirus (HPV) infection.

Histologically, the tumour is composed of papillary cores covered by benign squamous epithelium without koilocytic atypia.
Adenocarcinoma

**Definition**
A malignant neoplasm derived from the urothelium showing histologically pure glandular phenotype.

**Epidemiology**
Bladder adenocarcinoma is an uncommon malignant tumour accounting for less than 2% of all the malignant urinary bladder tumours (1192, 2612). It includes primary bladder adenocarcinoma and urachal carcinoma.

**Clinical features**
Adenocarcinoma of the urinary bladder occurs more commonly in males than in females at about 2.6:1, and affects adults with a peak incidence in the sixth decade of life (24, 878, 953, 1245, 1263, 1388, 1813, 2832). Haematuria is the most common symptom followed by dysuria, but mucusuria is rarely seen (953).

**Macroscopy**
Grossly, this tumour may be exophytic, papillary, sessile, ulcerating, or infiltrating and may exhibit a gelatinous appearance.

**Histopathology**
Histologically, pure adenocarcinoma of the bladder may show different patterns of growth (953). These include: enteric (colonic) type, (953) adenocarcinoma not otherwise specified (NOS) (953), signet ring cell (257, 952), mucinous (colloid) (953), clear cell (456, 2901), hepatoid (344), and mixed (953). The NOS

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**Fig. 2.55** Adenocarcinoma of bladder, colonic type. **A** In this view, the surface shows intestinal metaplastic changes that merge with the invaginating glandular elements. **B** In this illustration there are multiple glands embedded in a loose stroma.

**Fig. 2.56** **A** Signet ring cell carcinoma of bladder. The lamina propria exhibits diffuse infiltration of signet ring cells. **B** Adenocarcinoma. Hepatoid adenocarcinoma of the urinary bladder showing irregular areas of conventional adenocarcinoma (H&E).
Adenocarcinoma

A type consists of an adenocarcinoma with a non-specific glandular growth. The enteric type closely resembles adenocarcinoma of the colon. Tumours that show abundant mucin with tumour cells floating within the mucin are classified as mucinous or colloid type. The signet ring cell variant may be diffuse or mixed, can have a monocytoid or plasmacytoid phenotype, and an accompanying in situ component with numerous signet ring cells may be present [456]. An extremely rare variant of adenocarcinoma is the clear cell type (mesonephric), which consists of papillary structures with cytoplasmic cells that characteristically exhibit a HOBNAIL appearance [456]. The hepatoid type is also rare and consists of large cells with eosinophilic cytoplasm [344]. Finally, it is not uncommon to find a mixture of these growth patterns.

Adenocarcinoma in situ may be found in the urinary bladder alone or in combination with an invasive adenocarcinoma. The mucosa is replaced by glandular structures with definitive nuclear atypia. Three patterns are described and these are, papillary, cribriform and flat. A pure pattern is rarely seen, but various combinations of these are the rule [406]. There is no generally accepted grading system ascribed to adenocarcinoma of the bladder.

**Immunoprofile**

The immunohistochemical profile of these tumours that has been reported in the literature is variable and closely matches that of colonic adenocarcinomas [2572, 2629, 2777]. Reports of cytokeratin (CK) 7 positivity are variable ranging from 0-82%, while CK-20 is reported to be positive in most bladder adenocarcinomas. Villin has recently been reported to be positive in enteric type adenocarcinomas of the urinary bladder (2572). Another marker of interest is β-catenin, which has been reported to be of help in distinguishing primary adenocarcinomas of the bladder from metastatic colonic adenocarcinoma [2777].

**Differential diagnosis**

The differential diagnosis includes metastatic disease or direct extension, most commonly from colorectum and prostate. Secondary involvement is much more common than the primary adenocarcinoma of the bladder.

**Precursor lesions**

Most cases of adenocarcinoma of the urinary bladder are associated with longstanding intestinal metaplasia of the urothelium, such as may be seen in a non-functioning bladder [341, 660, 1504, 2898], obstruction [2379], chronic irritation [660, 1928, 2538] and cystocele. Adenocarcinoma arising in extrophy is felt to be secondary to the long-standing intestinal metaplasia common to this disease [919, 1677, 2521, 2791]. The risk of development of adenocarcinoma in extrophy is in the range of 4.1-7.1% [499]. Fifty-three patients with extrophy of the bladder were followed for more than 10 years, and none developed car-
Adenocarcinoma [499]. Cystitis glandularis is present in invasive adenocarcinoma ranging from 14-67% of cases [24,2612], but its role in the pathogenesis of invasive adenocarcinoma is not clear. However, in patients with pelvic lipomatosis, which harbors cystitis glandularis, adenocarcinoma may occur [1088,2862]. Adenocarcinoma may also arise in conjunction with villous adenomas, S. haematobium infestation, and endometriosis of the bladder [2885].

Somatic genetics
To date, few studies have examined the genetic alterations underlying adenocarcinoma of the bladder. A partial allelotype reported loss of chromosomal arm 9p (50%), 9q (17%), 17p (50%), 8p (50%) and 11p (43%) in 8 schistosomiasis-associated adenocarcinomas. Chromosomal arms 3p, 4p and 4q, 14q and 18q also showed LOH but no loss of 13q was seen [2380]. With the exceptions of a lower frequency of loss of 9q and 13q, this spectrum of chromosomal loss is similar to urorrhelial and squamous cell carcinoma of the bladder. LOH of 9p likely targets the p16/p14 tumour suppressor genes. The 17p LOH targets the p53 gene as a separate study reported 4/13 adenocarcinomas to have p53 point mutation [2784]. Further support for the observation of 18q loss is provided by a study that detected LOH of the D18S61 microsatellite marker in a patient’s adenocarcinoma and urine DNA [628].

Predictive factors
Clinical factors
Management of invasive adenocarcinoma of the bladder includes partial or radical cystectomy followed by consideration of chemotherapy or radiotherapy according to the extent of the lesion. Partial cystectomy is usually associated with a relatively high recurrence rate [2853]. Poor prognosis of this variant is associated with advanced stage at diagnosis. These tumours typically arise in the bladder base or dome, but can occur anywhere in the bladder. Primary vesical adenocarcinoma represents the most common type of cancer in patients with bladder extrophy. Signet-ring carcinoma is a rare variant of mucus-producing adenocarcinoma and will often produce linitis plastica of the bladder [454].

Morphologic factors
Stage is the most important prognostic factors for this disease [953]. However, the prognosis is poor since most adenocarcinomas present at advanced stage with muscle invasive disease and beyond (T2/T3). Survival at 5 years is 31% [953] -35% [551]. It is important to distinguish between urachal and non-urachal adenocarcinomas especially for treatment purposes. Some studies have suggested that non-urachal adenocarcinomas carry a worse prognosis [95,953,2612], but this was not confirmed. Among histologic types of adenocarcinoma, pure signet ring cell carcinoma carries the worst prognosis, otherwise histologic type has no prognostic significance [953].

Immunohistochemical markers
Little is known about genetic factors associated with prognosis of adenocarcinoma of the bladder. Proliferation indices of markers such as the nucleolar organizer region (AgNOR), Ki-67, and proliferating cell nuclear antigen (PCNA) are associated with grade and stage of nonurachal bladder adenocarcinomas [1994]. There is an increased incidence of local recurrence and distant metastasis in patients with a high Ki-67, PCNA, and AgNOR proliferation index.

**Table 2.05**

<table>
<thead>
<tr>
<th>Variant</th>
<th>Reference</th>
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<td>Adenocarcinomas, NOS</td>
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</tr>
<tr>
<td>Enteric (colonic type)</td>
<td>(953)</td>
</tr>
<tr>
<td>Signet ring cell</td>
<td>(257,952)</td>
</tr>
<tr>
<td>Mucinous</td>
<td>(953)</td>
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<tr>
<td>Clear cell</td>
<td>(456,2901)</td>
</tr>
<tr>
<td>Hepatoid</td>
<td>(344)</td>
</tr>
<tr>
<td>Mixed</td>
<td>(953)</td>
</tr>
</tbody>
</table>

Fig. 2.61 A Adenocarcinoma in situ of urinary bladder. B Adenocarcinoma in situ. Note columnar epithelium with nuclear anaplasia involving mucosal surface.
Urachal carcinoma

**Definition**
Primary carcinoma derived from urachal remnants. The vast majority of urachal carcinomas are adenocarcinomas; urothelial, squamous and other carcinomas may also occur.

**ICD-O code** 8010/3

**Epidemiology**
Urachal adenocarcinoma is far less common than non-urachal adenocarcinoma of the bladder. Most cases of urachal carcinoma occur in the fifth and sixth decades of life; the mean patient age is 50.6 years, which is about 10 years less than that for bladder adenocarcinoma. This disease occurs slightly more in men than in women, with a ratio, of about 1.8:1 (878,953,1230,1261,1263,1526,1813,2383,2832).

**Localization**
Urachal carcinomas arise from the urachus. Urachal remnants are reported to occur predominantly in the vertex or dome and the anterior wall, less frequently in the posterior wall, and they extend to the umbilicus (2343).

**Clinical features**
Hematuria is the most common symptom (71%), followed by pain (42%), irritative symptoms (40%), and umbilical discharge (2%) (878,953,1230,1261,1263,1526,1813,2383,2832). The patient may present with the suprapubic mass. Mucusuria occurs in about 25% of the cases (953), and its presence should raise the question of urachal mucous carcinoma.

**Macroscopy**
Urachal carcinoma usually involves the muscular wall of the bladder dome, and it may or may not destroy the overlying mucosa. The mass may be discrete, but it may involve the route of the urachal remnants, forming a relatively large mass that may invade the Retzius space and reach the anterior abdominal wall. Mucinous lesions tend to calcify, and these calcifications may be detected on plain X-ray films of the abdomen. The mucosa of the urinary bladder is not destroyed in early stages of the disease, but it eventually becomes ulcerated as the tumor reaches the bladder cavity. The cut surface of this tumor exhibits a glistening, light-tan appearance, reflecting its mucinous contents.
Staging
Although urachal adenocarcinoma has been staged as a bladder carcinoma using the TNM staging system which is difficult to apply because the majority of urachal adenocarcinomas are "muscle invasive". Hence, a specific staging system for this neoplasm has been proposed [2383].

Histopathology
This discussion pertains mainly to adenocarcinomas as the most common. Urachal adenocarcinomas are subdivided into mucinous, enteric, not otherwise specified, signet ring-cell, and mixed types; these subtypes are similar to those of adenocarcinoma of the urinary bladder. In one study with 24 cases of urachal carcinoma, 12 (50%) tumours were mucinous, seven (29%) were enteric, four (17%) were mixed, and one (4%) was a signet ring-cell carcinoma [953]. Mucinous carcinomas are characterized by pools or lakes of extracellular mucin with single cells or nests of columnar or signet ring-cells floating in it. The enteric type closely resembles a colonic type of adenocarcinoma and may be difficult to differentiate from it. Pure signet ring-cell carcinoma rarely occurs in the urachus; most commonly, signet ring-cell differentiation is present within a mucinous carcinoma. The cells of urachal adenocarcinoma stain for carcinoembryonic antigen [24,953], and Leu-M1 [24,953]. Criteria to classify a tumour as urachal in origin were initially established by Wheeler and Hill in 1954 [2811] and consisted of the following: (1) tumour in the dome of the bladder, (2) absence of cystitis cystica and cystitis glandularis, (3) invasion of muscle or deeper structures and either intact or ulcerated epithelium, (4) presence of urachal remnants, (5) presence of a suprapubic mass, (6) a sharp demarcation between the tumour and the normal surface epithelium, and (7) tumour growth in the bladder wall, branching into the Retzius space. These criteria, believed to be very restrictive, were modified by Johnson et al. [1230], who proposed the following criteria: (1) tumour in the bladder (dome), (2) a sharp demarcation between the tumour and the surface epithelium, and (3) exclusion of primary adenocarcinoma located elsewhere that has spread secondarily to the bladder. Bladder adenocarcinoma may be very difficult to rule out because it has the same histologic and immunohistochemical features as urachal adenocarcinoma does. Urachal adenocarcinoma may be associated with cystitis cystica and cystitis glandularis; the cystitis cystica or cystitis glandularis must show no dysplastic changes, however, because dysplastic changes of the mucosa or presence of dysplastic intestinal metaplasia would tend to exclude an urachal origin.

Precursor lesion
The pathogenesis of urachal adenocarcinoma is unknown. Although a urachal adenocarcinoma may arise from a villous adenoma of the urachus [1571], intestinal metaplasia of the urachal epithelium is believed to be the favoured predisposing factor [201].

Prognosis
Management of urachal adenocarcinoma consists of complete eradication of the disease. Partial or radical cystectomy, including the resection of the umbilicus, is the treatment of choice. Recurrences, are common, however, especially in cases in which a partial cystectomy is done [878,2853]. Examination of the surgical margins with frozen section has been advocated [878]. The 5 year survival rate has been reported to range from 25% [2813] to 61% [953].
Clear cell adenocarcinoma

**Definition**
Clear cell adenocarcinoma is a distinct variant of urinary bladder carcinoma that resembles its Müllerian counterpart in the female genital tract.

**ICD-O code**
8310/3

**Synonym**
Mesonephric carcinoma (2901).

**Epidemiology**
Clear cell adenocarcinomas of the urinary bladder are rare. Patients are typically females that range in age from 22 to 83 (mean 57 years), commonly presenting with hematuria and/or dysuria.

**Macroscopy**
Although the gross appearance is non-specific, frequently they grow as polypoid to papillary masses.

**Tumour spread and stage**
Clear cell adenocarcinomas may infiltrate the bladder wall and metastasize to lymph nodes and distant organs similarly to urothelial carcinomas. They should be staged using the TNM system for bladder cancer.

**Histopathology**
Clear cell adenocarcinomas have a characteristic morphology, showing one or more of the typical three morphologic patterns, tubulo-cystic, papillary and/or diffuse, the former being the most common. The tubules vary in size and may contain either basophilic and/or eosinophilic secretions. The papillae are generally small and their fibrovascular cores may be extensively hyalinized. When present, diffuse sheets of tumour cells are a minor component in most cases. The tumour cells range from flat to cuboidal to columnar and they may have either clear or eosinophilic cytoplasm or an admixture thereof. Hobnail cells are frequently seen but are only rarely conspicuous. Cytologic atypia is usually moderate to severe, frequently associated with a brisk mitotic activity. In some cases, clear cell adenocarcinomas may be associated with urothelial carcinoma or even rarely with adenocarcinoma non-special type (NOS). The differential diagnosis of clear cell adenocarcinoma includes most frequently nephrogenic adenoma, a benign reactive process, but also malignant tumours such as urothelial carcinoma with clear cells, metastatic clear cell renal carcinoma, cervical or vaginal clear cell adenocarcinoma, or rarely adenocarcinoma of the prostate secondarily involving the bladder.

**Precursor lesions**
Occasional clear cell adenocarcinomas have been associated with endometriosis or a Müllerian duct remnant, rare cases existed with urothelial dysplasia, and some clear cell adenocarcinomas arise in a diverticulum. Although exceptional cases have been reported to arise from malignant transformation of nephrogenic adenoma, this is a highly controversial area.

**Histogenesis**
In the past, bladder clear cell adenocarcinomas were thought to be of mesonephric origin, and were designated as mesonephric adenocarcinomas despite lack of convincing evidence for a mesonephric origin. As these tumours occur more frequently in women, they are histologically very similar to clear cell adenocarcinomas of the female genital tract, and they are occasionally associated with benign Müllerian epithelium.
Müllerian origin is postulated for some of them (640,876,1954). However, most clear cell adenocarcinomas probably originate from peculiar glandular differentiation in urothelial neoplasms as most bladder clear cell adenocarcinomas have not been associated with endometriosis, they have been diagnosed in patients with a previous history of urothelial carcinoma, and their immunohistochemical profile overlaps with that of urothelial carcinoma. In this setting it is presumed that aberrant differentiation which frequently occurs in high grade bladder cancer has an unusual morphology of clear cell adenocarcinoma in a small subset of patients (876,1954).

Prognosis and predictive factors
No long follow-up is available in many of these tumours. Cumulative experience from the literature indicates that clear cell adenocarcinoma may not be as aggressive as initially believed (85,640). Many of these tumours have an exophytic growth pattern, they may be diagnosed at an early stage and have a relative better prognosis. High stage tumours have a poor prognosis.

Villous adenoma

Definition
Villous adenomas is a benign glandular neoplasm of the urinary bladder which histologically mimics its enteric counterpart.

ICD-O code 8261/0

Epidemiology
Villous adenomas of the urinary bladder are rare with fewer than 60 cases reported. There is no apparent gender predominance. The tumour usually occurs in elderly patients (mean age, 65 years; range, 23-94 years).

Localization
It shows a predilection for the urachus, dome, and trigone of the urinary bladder.

Clinical symptoms
The patients often present with hematuria and/or irritative symptoms (430,2356). Cystoscopic examination often identifies an exophytic tumour.

Macroscopy
On gross examination the lesion is a papillary tumour that is indistinguishable from a papillary urothelial carcinoma.

Histopathology
Microscopically, the tumour is characterized by a papillary architecture with central fibrovascular cores, consisting of pointed or blunt finger-like processes lined by pseudostratified columnar epithelium. The epithelial cells display nuclear stratification, nuclear crowding, nuclear hyperchromasia, and occasional prominent nucleoli. The overall morphology of this lesion is similar to the colonic counterpart. Villous adenomas of the bladder often coexist with in situ and invasive adenocarcinoma. On limited biopsy specimens there may be only changes of villous adenoma. Therefore, the entire specimen should be processed to exclude invasive disease.

Immunoprofile
Villous adenomas of the bladder are positive for cytokeratin 20 (100% of cases), cytokeratin 7 (56%), carcinoembryonic antigen (89%), epithelial membrane antigen (22%), and acid mucin with alcian blue periodic acid-Schiff stain (78%) (430).

Prognosis
Patients with an isolated villous adenoma have an excellent prognosis. Progression to adenocarcinoma is rare.
Small cell carcinoma

Definition
Small cell carcinoma is a malignant neuroendocrine neoplasm derived from the urothelium which histologically mimics its pulmonary counterpart.

ICD-O code 8041/3

Clinical features
Gross haematuria is the most common presenting symptom in patients with small cell carcinoma (SCC) of the bladder. Other symptoms include dysuria or localized abdominal/pelvic pain (1531). Approximately 56% of patients will present with metastatic disease at the time of diagnosis. The most common locations for disease spread include: regional lymph nodes, 56%; bone, 44%; liver, 33%; and lung, 20% (2640). Peripheral (sensory) neuropathy may also be a clinical sign of metastatic disease and is attributed to the paraneoplastic syndrome associated with tumour production of antineuronal autoantibodies. The presence of anti-HU autoantibodies (IgG) is a specific marker of the paraneoplastic syndrome and should prompt careful evaluation for SCC (particularly in the lung) in a patient without a history of cancer (93). Electrolyte abnormalities such as hypercalcemia or hypophosphatemia, and ectopic secretion of ACTH have also been reported as part of the paraneoplastic syndrome associated with primary SCC of the bladder (2021,2182).

Localization and macroscopy
Almost all the small cell carcinomas of the urinary tract arise in the urinary bladder (2640). The tumour may appear as a large solid, isolated, polypoid, nodular mass with or without ulceration, and may extensively infiltrate the bladder wall. The vesical lateral walls and the dome are the most frequent topographies, in 4.7% they arise in a diverticulum (100).

Histopathology
All tumours are invasive at presentation (2640). They consist of small, rather uniform cells, with nuclear molding, scant cytoplasm and nuclei containing finely stippled chromatin and inconspicuous nucleoli. Mitoses are present and may be frequent. Necrosis is common and there may be DNA encrustation of blood vessels walls (Azzopardi phenomenon). Roughly 50% of cases have areas of urothelial carcinoma (1934) and exceptionally, squamous cell carcinoma and/or adenocarcinoma. This is important, because the presence of these differentiated areas does not contradict the diagnosis of small cell carcinoma. The neuroendocrine expression of this tumour is identified by many methods. In some papers, neuroendocrine granules are found with electron microscopy or histochemical methods, but in the majority of them, the immunohistochemical method is used. The neuronal-specific enolase is expressed in 87% of cases, and Chromogranin A only in a third of cases (2640). The diagnosis of small cell carcinoma can be made on morphologic grounds alone, even if neuroendocrine differentiation cannot be demonstrated. The differential diagnosis is metastasis of a small cell carcinoma from another site (very infrequent) (608), malignant lymphoma, lymphoepithelioma-like carcinoma, plasmacytoid carcinoma and a poorly differentiated urothelial carcinoma.

Histogenesis
In the spite of the low frequency of associated flat carcinoma “in situ” referred in the literature (14%) (2640), the high frequency of cytokeratin (CAM5.2 in 64%) expression in the small cell component supports the hypothesis of urothelial origin (60). Other hypotheses are the malignant transformation of neuroendocrine cells demonstrated in normal bladder (60), and the stem cell theory (254).

Somatic genetics
Data obtained by comparative genomic
hybridization suggest that urinary bladder small cell carcinoma is a genetically unstable tumour, typically exhibiting a high number of cytogenetic changes (2596). The most frequent changes included deletions of 10q, 4q, 5q, and 13q as well as gains of 8q, 5p, 6p, and 20q. High level amplifications, potentially pinpointing the location of activated oncogenes were found at 1p22-32, 3q26.3, 8q24 (including MYC), and 12q14-21 (including MDM2) (2596). Only one tumour was analyzed by cytogenetics (133). Complex and heterogeneous cytogenetic alterations were found in this tumour including rearrangements of the chromosomes 6, 9, 11, 13, and 18. The same tumour also showed a nuclear p53 accumulation.

**Prognosis and predictive factors**

**Clinical factors**

This tumour type is characterized by an aggressive clinical course with early vascular and muscle invasion. The overall 5-year survival rate for patients with small cell carcinoma of the bladder with local disease has been reported as low as 8% (8,2640). Overall prognosis has been shown to be related to the stage of disease at presentation; however, it has also been suggested that clinical stage is not independently associated with survival (1105,1587). The latter observation is based upon the theory that micrometastases are already present at the time of diagnosis in patients with clinically localized disease (1587). Age greater than 65, high TNM stage and metastatic disease at presentation are predictors of poor survival. Administration of systemic chemotherapy and cystectomy or radiotherapy, have variable success (182,1062,1587).

**Morphological factors**

No difference has been shown between tumours with pure or mixed histology. Tumour confined to the bladder wall may have a better prognosis (100,2640).

**Genetic factors**

The prognostic or predictive significance of cytogenetic or other molecular changes in small cell carcinoma of the urinary bladder is unknown. The immunohistochemical detection of p53 (77%) failed to mark cases with a poorer prognosis (2640).

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**Paraganglioma**

**Definition**

Paraganglioma of the bladder is a neoplasm derived from paraganglion cells in the bladder wall. They are histologically identical to paragangliomas at other sites.

**ICD-O code** 8680/1

**Synonym**

Phaeochromocytoma.

**Incidence**

These are rare tumours and by 1997 only about 200 cases had been reported (948). In the AFIP experience there were 77 bladder paragangliomas out of 16,236 bladder tumours (0.47%), but the commonly cited incidence is 0.06-0.10% (1420,1508,1845,2081).

**Clinical features**

These occur over a wide age range of 10-88 years with a mean in the forties (429,1845). They are a little more com-
mon in females by 1.4:1 (1845). The clinical triad of sustained or paroxysmal hypertension, intermittent gross hematuria and “micturition attacks” is the characteristic feature (1420,1845). These attacks consist of bursting headache, anxiety, tremulousness, pounding sensation, blurred vision, sweating and even syncope related to increased levels of catecholamines or their metabolites which can be found in serum or urine (1845). Some cases have been familial.

**Macroscopy**

An autopsy study has shown that paraganglia were present in 52% of cases (1115). They were present in any part of the bladder and at any level of the bladder wall. Most were in the muscularis propria and this is where most of the tumours are located. In 45 cases where the location was known, we found 38% in the dome, 20% in the trigone, 18% posterior wall, 13% anterior wall and the others in the bladder neck and lateral walls. Most of these are circumscribed or multinodular tumours, usually less than 4.0 cm in size. In one study there was an average diameter of 1.9 cm (1420).

**Histopathology**

Microscopically, the cells are arranged in discrete nests, the “Zellballen” pattern, separated by a prominent vascular network. Cells are round with clear, amphophilic or acidophilic cytoplasm and ovoid nuclei. Scattered larger or even bizarre nuclei are often present (1845). Mitoses are rare, and usually absent (1466). In some cases there may be striking resemblance to urothelial carcinoma. In about 10% of the cases, small neuroblast-like cells are present, usually immediately beneath the urothelium. By immunohistochemistry, bladder paragangliomas react as they do at other sites – negative for epithelial markers and positive for the neuroendocrine markers – chromogranin, synaptophysin and others. Flattened sustentacular cells can sometimes be highlighted in the periphery of the cell nests with S-100 protein. Ultrastructural features include dense core neurosecretory granules, usually having the typical morphology of catecholamine–secreting tumours with eccentric dense cores (948,1280).

**Prognosis and predictive factors**

The criteria for diagnosing malignant paraganglioma are metastasis and/or "extensive local disease" (1508). Long-term follow-up is always indicated because metastases have been known to occur many years later (948,1280, 1508). A recent study found that those tumours staged as T1 or T2 did not show any recurrences or metastases while those that were stage T3 or higher were at risk for both (429). A review of 72 AFIP cases accumulated since the initial 58 cases reported in 1971 (1466) has recently been done (unpublished data). Twelve of the 72 (16.7%) were judged to be malignant based upon the presence of metastasis or extension beyond the bladder. Four features appear to indicate an increased potential for malignant behaviour:

1. Younger age: there were 8 cases in the second decade of life and 5 of these were malignant.
2. Hypertension: this was seen in 50% of malignant cases and 12% of the benign ones.
3. Micturition attacks: these were also seen in 50% of malignant cases and 12% of benign ones.
4. Invasive dispersion through the bladder wall. The malignant tumours usually demonstrated widespread dispersion through the bladder wall, sometimes with fragmentation of muscle fascicles by tumour nests. This was rarely seen in those that proved to be benign.

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**Fig. 2.71** Paraganglioma. 
A Paraganglioma with circumscribed growth pattern. 
B Paraganglioma with dissection through the muscularis propria. 
C Paraganglioma with circumscribed growth pattern.

**Fig. 2.72** Paraganglioma of the urinary bladder. 
Large paraganglioma adjacent to the wall of the urinary bladder.
Carcinoid

Definition
Carcinoid is a potentially malignant neuroendocrine neoplasm derived from the urothelium which histologically is similar to carcinoid tumours at other locations.

ICD-O code 8240/3

Epidemiology
Less than two-dozen cases of carcinoid tumours of the urinary bladder have been reported [343,449,480,1068,2485,2527,2768,2865]. The tumour usually occurs in elderly patients (mean age, 56 years; range, 29-75 years), with slight male predominance (the male-to-female ratio, 1.8:1).

Clinical features
Hematuria is the most common clinical presentation, followed by irritative voiding symptoms. Association with carcinoid syndrome has not been reported.

Macroscopy
The tumours are submucosal with a predilection for the trigone of the bladder, and range in size from 3 mm-3 cm in the largest dimension. The tumour often presents as a polypoid lesion upon cystoscopic examination. One case arose in an ileal neobladder [803]. Coexistence of carcinoid with other urothelial neoplasia, such as inverted papilloma [2485] and adenocarcinoma [449], has been reported.

Histopathology
Carcinoid tumours of the bladder are histologically similar to their counterparts in other organ sites. The tumour cells have abundant amphophilic cytoplasm and arranged in an insular, acini, trabecular, or pseudoglandular pattern in a vascular stroma. An organoid growth pattern, resembling that seen in paraganglioma, can be appreciated. The nuclei have finely stippled chromatin and inconspicuous nucleoli. Mitotic figures are infrequent, and tumour necrosis is absent. The tumours show immunoreactivity for neuroendocrine markers (neuron-specific enolase, chromogranin, serotonin, and synaptophysin) and cytokeratin (AE1 and 3). The tumours are positive for the argyrophil reaction by Grimelius silver stains and argentaffin reaction by Fontana-Masson stains. Ultrastructural examinations demonstrate characteristic uniform, round, membrane-bound, electron-dense neurosecretory granules. Flow cytometric studies revealed an aneuploid cell population in one case [2768].

Differential diagnosis
This includes paraganglioma, nested variant of urothelial carcinoma and metastatic prostatic carcinoma.

Prognosis and predictive factors
More than 25% of patients will have regional lymph node or distant metastasis [2527] but majority are cured by excision.
Rhabdomyosarcoma

**Definition**
Rhabdomyosarcoma is a sarcoma occurring in the urinary bladder that recapitulates morphologic and molecular features of skeletal muscle.

**ICD-O code** 8900/3

**Epidemiology**
They are the most common urinary bladder tumours in childhood and adolescence. Almost all bladder rhabdomyosarcomas are of embryonal subtype, whereas the genetically distinct alveolar subtype is extremely rare in this site (1887). In adults rhabdomyosarcoma is rare and usually of the pleomorphic type.

**Macroscopy**
Growth pattern of embryonal rhabdomyosarcoma in urinary bladder has two basic forms with prognostic impact: polypoid, mostly intraluminal tumours associated with a favourable prognosis (botryoid subtype) and deeply invasive growing tumours involving the entire bladder wall and usually adjacent organs showing a worse prognosis.

**Histopathology**
Tumour cells of embryonal rhabdomyosarcoma are usually small, round cells, often set in a myxoid stroma. Some cells may have classic rhabdomyoblastic appearance with abundant eosinophilic cytoplasm and cross striations. Botryoid subtype of embryonal rhabdomyosarcoma has a condensation of tumour cells beneath the covering surface epithelium, called the cambium layer. Deeper parts of the tumours are often hypocellular. The botryoid subtype of embryonal rhabdomyosarcoma is the end of a spectrum of polypoid growing embryonal rhabdomyosarcomas sharing a similar favourable prognosis (1482). Primarily deep invasive growing tumours of the urinary bladder wall have usually a low degree of differentiation and are associated to a similar worse prognosis as seen for embryonal rhabdomyosarcoma of prostate.

Immunohistochemically, the tumour cells express myogenin (myf4) and MyoD1 in the nucleus (612,1404). This is assumed to be specific for a skeletal muscle differentiation. Highly differentiated tumour cells can lack myogenin expression. Desmin and pan-actin (HHF35) can also be detected in almost all rhabdomyosarcomas but it is not specific. Staining for myosin and myoglobin can be negative because it is usually found only in well differentiated tumour cells. Recurrences of embryonal rhabdomyosarcoma can show a very high degree of differentiation forming round myoblasts.
Leiomyosarcoma

Definition
Leiomyosarcoma is a rare malignant mesenchymal tumour that arises from urinary bladder smooth muscle.

ICD-O code 8890/3

Epidemiology and etiology
Although leiomyosarcoma is the most common sarcoma of the urinary bladder it accounts for much less than 1% of all bladder malignancies. Males are more frequently affected than females by over 2:1 (1639,1734,2543). This sarcoma occurs primarily in adults in their 6th to 8th decade. Several cases of leiomyosarcoma of the bladder have occurred years after cyclophosphamide therapy (2039,2253).

Localization
Leiomyosarcoma can occur anywhere within the bladder, and very rarely can involve the ureter or renal pelvis (947, 1816).

Clinical features
The vast majority of patients present with haematuria, and on occasion, a palpable pelvic mass, abdominal pain or urinary tract obstruction may be present.

Macroscopy
Leiomyosarcoma of the urinary bladder is typically a large, infiltrating mass with a mean size of 7 cm. High grade leiomyosarcoma frequently exhibits gross and microscopic necrosis.

Histopathology
Histopathologic examination reveals a tumour composed of infiltrative interlacing fascicles of spindle cells. Grading of leiomyosarcoma is based on the degree of cytologic atypia. Low grade leiomyosarcoma exhibits mild to moderate cytologic atypia, and has mitotic activity less than 5 mitoses per 10 HPF. In contrast, high grade leiomyosarcoma shows marked cytologic atypia, and most cases have greater than 5 mitoses per 10 HPF. Immunohistochemically, leiomyosarcoma stains with antibodies directed against actin, desmin and vimentin, and are negative for epithelial markers (1410,1639, 1734,2817).

Leiomyoma can be morphologically separated from leiomyosarcoma based on its small size, low cellularity, circumscription, and lack of cytologic atypia (1639). Reactive spindle cell proliferations such as inflammatory pseudotumour or postoperative spindle cell nodule/tumour can be difficult to distinguish from leiomyosarcoma (1572,2889). Leiomyosarcoma exhibits greater cytologic atypia, abnormal mitoses, and an arrangement in compact cellular fascicles in contrast to reactive spindle cell proliferations, which have a loose vascular myxoid background. However, myxoid change can occur in leiomyosarcoma (2899).

Sarcomatoid carcinoma can resemble leiomyosarcoma but is usually associated with a malignant epithelial component or exhibits cytokeratin positivity.

Prognosis
Although previous reports suggest that 5-year survival after partial or radical cystectomy approaches 70%, the largest recent study indicates that 70% of patients with leiomyosarcoma developed recurrent or metastatic disease, resulting in death in nearly half (1639).
**Angiosarcoma**

**Definition**
Angiosarcoma of the urinary bladder is a very rare sarcoma that arises from the endothelium of blood vessels.

**ICD-O code** 9120/3

**Clinical features**
Only 10 cases of urinary bladder angiosarcoma have been reported, all as case reports (699). Males are more frequently affected than females, and tumours occur in adults with a mean age at diagnosis of 55 years. Patients present with hematuria, and approximately a third of cases are associated with prior radiation to the pelvis, either for gynecologic malignancies or prostate cancer (699, 1874).

**Macroscopy**
Angiosarcoma of the bladder is typically a large tumour but can be as small as 1 cm. Most tumours exhibit local or distant extension beyond the bladder at the time of diagnosis.

**Histopathology**
Histopathologic features consist of anastomosing blood-filled channels lined by cytologically atypical endothelial cells. Some angiosarcomas have solid areas, and epithelioid features can be present (2322). Urinary bladder angiosarcoma stains positively with the immunohistochemical markers of endothelium including CD31 and CD34. The only epithelioid angiosarcoma of the urinary bladder reported to date was negative for cytokeratin, but some epithelioid angiosarcomas at other sites can be cytokeratin positive. Angiosarcoma must be distinguished from haemangioma of the bladder. Haemangioma of the bladder is typically small (usually less than 1 cm), and nearly 80% are of the cavernous type (431). Urinary haemangioma lacks cytologic atypia and the anastomosing and solid areas of angiosarcoma. Pyogenic granuloma is another benign vascular proliferation that very rarely occurs in the bladder, and is composed of closely spaced capillaries lined by bland endothelium which may show mitotic activity (90). Kaposi sarcoma may involve the urinary bladder and should be considered in the differential diagnosis, especially in immunocompromised patients (2183, 2866). Rarely, high grade urothelial carcinoma can mimic angiosarcoma but the identification of a clearly epithelial component as well as immunohistochemistry can be diagnostic (2085).

**Prognosis**
Urinary bladder angiosarcoma is a very aggressive neoplasm, and approximately 70% of patients die within 24 months of diagnosis (699).
Osteosarcoma

Definition
A malignant mesenchymal tumour showing osteoid production.

ICD-O code 9180/3

Epidemiology
Most osteosarcomas of the urinary bladder occurred in male patients (male to female ratio: 4:1), with an average age of 60-65 years [215,863,2900].

Etiology
One case of bladder osteosarcoma occurred 27 years after radiation therapy for urothelial carcinoma [754]. A few patients had concurrent urinary schistosomiasis [2900].

Localization
Most osteosarcomas occurred in the urinary bladder, especially in the trigone region [2900]. Anecdotal cases have been reported in the renal pelvis [655].

Clinical features
Haematuria, dysuria, urinary frequency, and recurrent urinary tract infections are the most common presenting symptoms. Pelvic pain and/or palpable abdominal mass are less frequent.

Macroscopy
Osteosarcoma of the urinary bladder typically presents as a solitary, large, polypoid, gritty, often deeply invasive, variably haemorrhagic mass. Tumour size varies between 2 and 15 cm (median: 6.5 cm) [215,863,2900].

Histopathology
Histologically, the tumour is a high grade, bone-producing sarcoma. Foci of chondrosarcomatous differentiation and/or spindle cell areas may also be observed [215,2900]. Variably calcified, woven bone lamellae are rimmed by malignant cells showing obvious cytologic atypia (as opposed to stromal osseous metaplasia occurring in some urothelial carcinomas [655]). A recognizable malignant epithelial component should be absent, allowing discrimination from sarcomatoid carcinoma [2057], which is the most important differential diagnosis.

Prognosis
Osteosarcoma of the urinary tract is an aggressive tumour with poor prognosis. A majority of patients have advanced stage (pT2 or higher) disease at presentation and die of tumour within 6 months, most from the effects of local spread (urinary obstruction, uremia, secondary infection, etc.) [863,2900]. Metastases often occurred late in the course of the disease, mainly in lungs [215,2900]. The stage of the disease at diagnosis is the best predictor of survival.
Malignant fibrous histiocytoma

J. Cheville

Definition
Malignant fibrous histiocytoma (MFH) is a malignant mesenchymal neoplasm occurring in the urinary bladder composed of fibroblasts and pleomorphic cells with a prominent storiform pattern.

ICD-O code 8830/3

Synonym
Undifferentiated high grade pleomorphic sarcoma.

Epidemiology
Malignant fibrous histiocytoma is one of the most frequent soft tissue sarcomas, and in some series, the second most frequent sarcoma of the urinary tract in adults (1410). It is difficult to determine the incidence of urinary bladder malignant fibrous histiocytoma as it is likely that several tumours previously reported as malignant fibrous histiocytoma are sarcomatoid urothelial carcinoma. Malignant fibrous histiocytoma more frequently affects men, and is most common in patients in their 5th to 8th decade.

Clinical features
Patients present with haematuria.

Macroscopy
Similar to other sarcomas of the urinary bladder, most malignant fibrous histiocytomas are large but tumours as small as 1 cm have been reported.

Histopathology
All subtypes of malignant fibrous histiocytoma have been described involving the bladder including myxoid, inflammatory, storiform-fascicular, and pleomorphic (809,1410,1935). Malignant fibrous histiocytoma must be separated from sarcomatoid urothelial carcinoma as well as reactive spindle cell proliferations of the bladder. The much more commonly encountered sarcomatoid urothelial carcinoma can be associated with a malignant epithelial component, and stains positively for the immunohistochemical markers of epithelial differentiation such as cytokeratin (1038,1555,2038). In contrast, malignant fibrous histiocytoma is negative for cytokeratin, and can stain for alpha-1-antichymotrypsin, and CD68. Reactive spindle cell proliferations lack the cytologic atypia of malignant fibrous histiocytoma.

Prognosis
The rarity of malignant fibrous histiocytoma makes it difficult to assess the biologic behaviour of these tumours. However, from the limited reports, malignant fibrous histiocytoma of the bladder appears aggressive with high local recurrence rates and metastases similar to malignant fibrous histiocytoma at other sites (809). Treatment consists of resection, systemic chemotherapy and external beam radiation. The only patient with myxoid malignant fibrous histiocytoma of the bladder has been free of tumour following surgical resection, local radiation and systemic chemotherapy for 3 years (809).
Leiomyoma

**Definition**
A benign mesenchymal tumour occurring in the bladder wall showing smooth muscle differentiation.

**ICD-O code**
8890/0

**Epidemiology**
Leiomyoma of the urinary bladder is the most common benign mesenchymal neoplasm of the urinary bladder (908, 1255, 1338). Unlike sarcomas of the bladder, there is a predominance of females (908). There is a wide age range from children to the elderly, but the vast majority of patients are middle-aged to older adults.

**Clinical features**
Patients present most frequently with obstructive or irritative voiding symptoms, and occasionally haematuria.

**Macroscopy**
Most leiomyomas are small with a mean size less than 2 cm (1338). Tumours up to 25 cm have been reported (908). Grossly, the tumours are circumscribed, firm, and lack necrosis.

**Histopathology**
Histopathological features include well formed fascicles of smooth muscle. Leiomyoma of the bladder is circumscribed with low cellularity, lack of mitotic activity and bland cytologic features (1639). They are immunoreactive to smooth muscle actin and desmin.

**Prognosis**
Patients are treated by transurethral resection for small tumours, and open segmental resection for larger tumours. Surgical removal is curative in all cases.

Other non-epithelial tumours

Malignant mesenchymal neoplasms such as malignant peripheral nerve sheath tumour, liposarcoma, chondrosarcoma and Kaposi sarcoma can very rarely involve the bladder (1410). The diagnosis of primary liposarcoma and malignant peripheral nerve sheath tumour of the bladder requires that bladder involvement by direct extension from another site be excluded. In the case of primary bladder osteosarcoma and chondrosarcoma, sarcomatoid carcinoma must be excluded. Solitary fibrous tumour of the bladder of the urinary bladder has recently been recognized (159, 502, 2808). Solitary fibrous tumour of the bladder occurs in older patients who present with pain or haematuria. Two of the seven cases that have been reported were incidental findings (2808). The tumour is typically a polypoid submucosal mass. Histopathologic features include spindle cells arranged haphazardly in a variably collagenous stroma. Dilated vessels reminiscent of haemangiopericytoma are present. Solitary fibrous tumour at other sites can act in an aggressive manner, but all solitary fibrous tumours of the bladder have had a benign course, although the number of cases is small, and follow-up has been short term in several cases.
Granular cell tumour

**Definition**
A circumscribed tumour consisting of nests of large cells with granular eosinophilic cytoplasm due to abundant cytoplasmic lysosomes.

**ICD-O code** 9580/0

**Epidemiology**
This tumour is rarely seen in the urinary bladder. The 11 cases reported in the literature and the 2 cases in the Bladder Tumour Registry of the Armed Forces Institute of Pathology occurred in adult patients from 23-70 years of age (88,779,1631,1752,1821,1949, 2351,2881). There is no gender predilection.

**Macroscopy**
The tumours are usually solitary, well circumscribed and vary in size up to 12 cm.

**Histopathology**
Microscopically, the cells have abundant granular eosinophilic cytoplasm and vesicular nuclei. S-100 protein can be identified in the tumour cells (2490). A congenital granular cell tumour of the gingiva with systemic involvement including urinary bladder has been reported (2011).

**Prognosis**
To date, only one malignant granular cell tumour of the bladder has been described (2153).

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Neurofibroma

**Definition**
A benign mesenchymal tumour occurring in a urinary bladder wall consisting of a mixture of cell types including Schwann cell, perineurial like cells and fibroblasts.

**ICD-O code** 9540/0

**Epidemiology**
Neurofibromas of the urinary bladder occur infrequently; fewer than 60 cases have been reported. The tumours typically occur in young patients with neurofibromatosis type 1. The mean age at diagnosis is 17 years, and the male-to-female ratio is 2.3:1 (434).

**Clinical features**
Patients typically exhibit physical stigmata of neurofibromatosis type 1. The urinary bladder is the most common site of genitourinary involvement in neurofibromatosis, and involvement of the bladder is often extensive, necessitating cystectomy in approximately one-third of cases. Clinical signs include hematuria, irritative voiding symptoms, and pelvic mass.

**Macroscopy**
The tumours frequently are transmural, showing a diffuse or plexiform pattern of growth.

**Histopathology**
Histologically, the tumours are usually of the plexiform and diffuse type. Neurofibroma of the bladder is characterized by a proliferation of spindle cells with ovoid or elongate nuclei in an Alcian blue positive, variably collagenized matrix. Cytoplasmic processings of tumour cells are highlighted on immunostaining for S-100 protein. Differential diagnostic considerations include low grade malignant peripheral nerve sheath tumour, leiomyoma, post-operative spindle nodule, inflammatory pseudotumour, leiomyosarcoma, and rhabdomyosarcoma. It is critical to distinguish neurofibroma of atypical or cellular type from malignant peripheral nerve sheath tumour. Atypical neurofibromas lack mitotic figures or appreciable MIB-1 labeling. Cellular neurofibromas lack significant cytologic atypia or mitotic figures. The finding of rare mitotic figures in a cellular neurofibroma is not sufficient for a diagnosis of malignancy (434). Adequate sampling is critical when increased cellularity is noted in superficial biopsies.

**Prognosis**
Long-term urinary complications include bladder atony, neurogenic bladder, and recurrent urinary tract infection with hematuria. Only 4 tumours (7%) underwent malignant transformation, none of these occurred in children (434,1737).
Malignant melanoma

Definition
Malignant melanoma is a malignant melanocytic neoplasm which may occur in the urinary bladder as a primary or, more frequently, as metastatic tumour.

ICD-O code
8720/3

Epidemiology
Melanoma primary in the bladder has been reported in less than twenty patients (1303). All have been adults and men and women have been equally affected.

Clinical features
Gross hematuria is the most frequent presenting symptom but some have presented with symptoms from metastases (2550). The generally accepted criteria for determining that melanoma is primary in the bladder are: lack of history of a cutaneous lesion, failure to find a regressed melanoma of the skin with a Woods lamp examination, failure to find a different visceral primary, and pattern of spread consistent with bladder primary.

Macroscopy
Almost all of the tumours have appeared darkly pigmented at cystoscopy and on gross pathologic examination. Their sizes ranged from less than 1 cm to 8 cm.

Histopathology
Microscopically, the great majority of tumours have shown classic features of malignant melanoma: pleomorphic nuclei, spindle and polygonal cytoplasmic contours, and melanin pigment. Pigment production is variable and may be absent; one example of clear cell melanoma has been reported. A few of the tumours have been associated with melanosis of the vesical epithelium (431,1000,1098,1474). Electron microscopy has shown melanosomes in several of the tumours.

Prognosis
Two-thirds of the patients have died of metastatic melanoma within 3 years of diagnosis; follow up of those alive at the time of the report has been less than 2 years.

Haemangioma

Definition
Haemangioma of the urinary bladder is a rare benign tumour that arises from the endothelium of blood vessels.

ICD-O code
9120/0

Epidemiology
It may be associated with the Klippel-Trenaunay-Weber or Sturge-Weber syndromes (1000,1098,1474). The mean age at presentation is 58 years (range, 17-76 years); the male/female ratio is 3.7:1 (431).

Clinical features
Patients often present with macroscopic hematuria and cystoscopic findings are usually non-specific. However, cystoscopic findings of a sessile, blue, multiloculated mass are highly suggestive of haemangioma; the cystoscopic differential diagnostic considerations for pigmented raised lesions include endometriosis, melanoma, and sarcoma. Accurate diagnosis requires biopsy confirmation.

Macroscopy
The tumour has a predilection for the posterior and lateral walls, the lesion is non descript but may be haemorrhagic.

Histopathology
Three histologic types of haemangiomas are reported. Cavernous haemangioma is more common than capillary and arteriovenous haemangiomas. These tumours are morphologically identical to their counterparts in other organ sites, and the same criteria should be used for the diagnosis. Haemangioma is distinguished from angiosarcoma and Kaposi sarcoma by its lack of cytologic atypia and well circumscribed growth. Exuberant vascular proliferation may be observed in papillary cystitis and granulation tissue; but these lesions contain prominent inflammation cells, which is not seen or is less pronounced in haemangioma.

Histogenesis
Haemangioma of the urinary bladder arises from embryonic angioblastic stem cells (431,1000,1098,1474).
Lymphomas

Definition
Malignant lymphoma is a malignant lymphoid neoplasm which may occur in the urinary bladder as a primary or part of a systemic disease.

Epidemiology
Lymphomas constitute about 5% of non-urothelial tumours of the urinary tract. More than 90% affect the bladder (1297), constituting less than 1% of bladder neoplasms (86,106,530). Secondary lymphoma of the bladder is common (12-20%) in advanced stage systemic lymphoma, shows a slight male predominance and may occur in children (885, 1297). Primary lymphomas of the bladder (1297,1946,2793) and urethra (127, 398,1040,1414) are rare, affect mainly females (65-85%) and occur at an age of 12 - 85 (median 60) years. In one series only 20% of cases were primary lymphomas (1297).

Etiology
The etiology of urinary tract lymphomas is unclear. Chronic cystitis is regularly encountered in MALT lymphoma of the bladder (1297,1402,2034), but less frequently (20%) in other lymphomas (1946). EBV and HIV infection have been reported in rare high grade urinary tract lymphoma (UTL) (1257,1692,1947). Schistosomiasis was associated with a T-cell lymphoma of the bladder (1820). Posttransplant lymphoproliferative disease restricted to the ureter allograft may occur after renal transplantation (591,2360).

Clinical features
The most frequent symptom of urinary tract lymphomas is gross hematuria, followed by dysuria, urinary frequency, nocturia and abdominal or back pain (1297,1946). Fever, night sweats, and weight loss or ureteral obstruction with hydronephrosis and renal failure occur almost only in patients with secondary urinary tract lymphomas due to retroperitoneal disease. Antecedent or concurrent MALT lymphomas in the orbit (1297) and stomach (1396), and papillary urothelial tumours rarely occur (2034).

Urinary tract lymphomas affect the renal pelvis, ureter, bladder and urethra. Primary urinary tract lymphomas are confined to the urinary tract, while secondary lymphoma results from disseminated lymphoma/leukaemia. Secondary bladder lymphoma as the first sign of disseminated disease is termed "nonlocalised lymphoma" with a much better prognosis than "secondary [recurrent] lymphoma" in patients with a history of lymphoma (1297).

Macroscopy
Bladder lymphomas may form solitary (70%) or multiple (20%) masses or diffuse thickening (10%) of the bladder wall. Ulceration is rare (<20%) in primary, but common in secondary urinary tract lymphomas. Frankly haemorrhagic changes have been observed (637). Lymphoma of the ureter may form nodules or a diffuse wall thickening. In the urethra, lymphomas often present as a caruncle (127).

Histopathology
Among primary urinary tract lymphomas, low grade MALT lymphoma is the most frequent in the bladder (27,47,1297, 1402,2034,2793). Reactive germinal centers are consistently present while lymphoepithelial lesions occur in only 20% of cases associated with cystitis cystica or cystitis glandularis. Other bladder lymphomas, like Burkitt lymphoma (1692), T-cell lymphoma (1820), Hodgkin lymphoma (1243,1623) and plasmacytomas (398,1730) are very rare. In the ureter and renal pelvis, primary MALT lymphoma (1018), diffuse large B-cell lymphoma (238,1035) and posttransplant lymphoproliferative disease (591,2360) have been reported. In the urethra, several diffuse large B-cell lymphomas (1040) and single mantle cell (1259) and T-cell NOS lymphomas (1257) and plasmacytoma (1473) were described. Among secondary urinary tract lymphomas, diffuse large B-cell lymphoma is the single most frequent histological subtype, followed by follicular, small cell, low grade MALT, mantle cell (1297,1946) Burkitt (1946) and Hodgkin lymphoma (1702,1946,2635).

Histogenesis (postulated cell of origin)
The histogenesis of urinary tract lymphomas is probably not different from that of other extranodal lymphomas.

Somatic genetics and genetic susceptibility
Genetic findings specific to urinary tract lymphomas have not been reported.

Prognosis and predictive factors
Primary MALT of the urinary tract has an excellent prognosis after local therapy with virtually no tumour-related deaths (127,1040,1297,2034,2793). "Nonlocalised lymphomas" and secondary [recurrent] lymphomas of the bladder have a worse prognosis (median survival 9 years and 0.6 year, respectively) (1297), comparable to patients with advanced lymphomas of respective histological type elsewhere.
Metastatic tumours and secondary extension in urinary bladder

Definition
Tumours of the urinary bladder that originate from an extravesical, non-urothelial tract neoplasm.

Localization
The most frequent locations of metastases to the urinary bladder are the bladder neck and the trigone.

Clinical features
Metastases or, in most cases, direct extension of colonic carcinomas to the bladder are most frequent at 21%, followed by carcinomas of the prostate (19%), rectum (12%), and uterine cervix (11%). Much less frequent is metastatic spread to the urinary bladder of neoplasias of the stomach, skin, breast, and lung at 2.5-4% (184).

Macroscopy
The lesions may mimic a primary urothelial carcinoma or may manifest as multiple nodules.

Histopathology
Some metastatic or secondary tumours, such as malignant lymphomas, leukemias, malignant melanomas, or prostatic adenocarcinomas may be diagnosed by routine microscopy. However, tumours with less characteristic histological features, poorly or undifferentiated high grade tumours require immunohistochemical work-up [849,1954,2415,2708,2777]. Multifocality and prominent vascular involvement in tumours with unusual morphology should raise suspicion of metastatic tumours.

Fig. 2.85 A Metastatic prostate cancer to urinary bladder. B Metastatic colon cancer to urinary bladder.

Fig. 2.86 Metastatic breast cancer to urinary bladder.
Metastatic tumours and secondary extension in urinary bladder

Fig. 2.87 Metastatic tumours to the urinary bladder. A Well differentiated adenocarcinoma of the colon infiltrating the bladder. B Moderately differentiated colonic adenocarcinoma infiltrating the bladder with extensive areas of necrosis. C Prostatic carcinoma with neuroendocrine features. D Well differentiated carcinoma of the prostate infiltrating the bladder.
Tumours of the renal pelvis and ureter

Definition
Benign and malignant tumours arising from epithelial and mesenchymal elements of the renal pelvis and ureter.

Epidemiology
Tumours of the ureter and renal pelvis account for 8% of all urinary tract neoplasms and of these greater than 90% are urothelial carcinomas (1582). The incidence of these tumours is 0.7 to 1.1 per 100,000 and has increased slightly in the last 30 years. There is a male to female ratio of 1.7 to 1 with an increasing incidence in females. As with bladder cancer, tumours of the ureter and renal pelvis are more common in older patients with a mean age of incidence of 70 years (1834).

Malignant epithelial tumours
Urothelial neoplasms
Clinical features
Malignant tumours of the pelvicalyceal system are twice as common as those of the ureter and multifocality is frequent (1655). 80% of tumours arise following diagnosis of a bladder neoplasm (1910) and in 65% of cases, urothelial tumours develop at other sites (183). Haematuria and flank pain are the chief presenting symptoms.

Epidemiology of urothelial renal pelvis cancer
Renal pelvis is a part of the lower urinary tract, which consists also of ureter, urinary bladder and urethra. As in the urinary bladder, a majority of renal pelvis tumours are urothelial carcinomas. (602). Tumours of renal pelvis are rare. In males, they constitute 2.4% of tumours of lower urinary tract and 0.1% of all cancers in Europe. Corresponding figures for North America are 2.7% and 0.1%. In females, cancer of the renal pelvis
makes 4.6% of lower urinary tract tumours and 0.07% of all cancers in Europe, and 5.2% and 0.07% respectively in North America.

The highest incidence rates of renal pelvis tumours are observed in Australia, North America and Europe, while the lowest rates are noted in South and Central America and in Africa. The highest rates in males in 1990s were observed in Denmark (1.65/105), Ferrara Province in Italy (1.45/105), Hiroshima, Japan (1.41/105), and in Mallorca, Spain (1.38/105). In females, the highest incidence rates were noted in New South Wales and Queensland in Australia (1.34 and 1.03/105 respectively), Denmark (0.95/105), Louisiana (among Blacks), USA (0.79/105), and Iceland (0.79/105) (2016). Although limited information is available about changes of renal pelvis cancer in time, available data from US show that in 1970s and 1980s renal pelvis cancer incidence rates rose by approximately 2.2% per year in both males and females (602).

Etiology of urothelial renal pelvis cancer

Tobacco smoking

Similar to cancers of the urinary bladder, the main risk factor for renal pelvis tumours is tobacco smoking (1680). The relationship between tobacco smoking and renal pelvis tumours was reported already in 1970s (2324), and confirmed by several authors (1215, 1681, 2245). The risk increases with increasing lifetime consumption, as well as with increasing intensity of smoking, and is similar in both sexes (1215, 1681).

Analgetics

Another proven risk factor for cancer of the renal pelvis is long-term use of analgesics, particularly phenacetin. Use of analgesics increases risk of renal pelvis tumours by 4-8 times in males and 10-13 times in women, even after elimination of the confounding effect of tobacco smoking (1668, 1680, 2245).

Occupational exposure

Several occupations and occupational exposures have been reported to be associated with increased risk of renal pelvis tumours (1215). The highest risk was found for workers of chemical, petrochemical and plastic industries, and also exposed to coke and coal, as well as to asphalt and tar (1215).

Other risk factors include papillary necrosis, Balkan nephropathy, thorium containing radiologic contrast material, urinary tract infections or stones (922, 1227, 1260, 1583).

Macroscopy

Tumours may be papillary, polypoid,
nodular, ulcerative or infiltrative. Some tumours distend the entire pelvis while others ulcerate and infiltrate, causing thickening of the wall. A high grade tumour may appear as an ill defined scirrhouss mass that involves the renal parenchyma, mimicking a primary renal epithelial neoplasm. Hydronephrosis and stones may be present in renal pelvic tumours while hydrourerter and/or stricture may accompany ureteral neoplasms. Multifocality must be assessed in all nephroureterectomy specimens.

Tumour staging
There is a separate TNM staging system for tumours of the renal pelvis and ureter (944,2662). Slight differences based on anatomical distinctions exist in the pT3 designation of renal pelvis and ureteral tumours.

Histopathology
The basic histopathology of renal pelvis urothelial malignancies mirrors bladder urothelial neoplasia and may occur as papillary non-invasive tumours (papillary urothelial neoplasm of low malignant potential, low grade papillary carcinoma or high grade papillary carcinoma), carcinoma-in-situ and invasive carcinoma. The entire morphologic spectrum of vesical urothelial carcinoma is seen and tumour types include those showing aberrant differentiation (squamous and glandular), unusual morphology (nested, microcystic, micropapillary, clear cell and plasmacytoid) and poorly differentiated carcinoma (lymphoepithelioma-like, sarcomatoid and giant cell) (355,399, 656,727,2706). Concordance of aberrant differentiation, unusual morphology or undifferentiated carcinoma with conventional invasive poorly differentiated carcinoma is frequent.

Grading
The grading system for urothelial tumours is identical to that employed for bladder tumours.

Genetic susceptibility
Familial history of kidney cancer (2245) is generally considered a risk factor. Urothelial carcinomas of the upper urothelial tract occur in the setting of hereditary nonpolyposis colorectal cancer (HNPCC) syndrome (Lynch syndrome II) (251).

Genetics
Urothelial carcinomas of the renal pelvis, ureter and urinary bladder share similar genetic alterations (734,2197). Deletions on chromosome 9p and 9q occur in 50-75% of all patients (734,993,2197,2554) and frequent deletions at 17p in addition to p53 mutations, are seen in advanced invasive tumours (321,993). 20-30% of all upper urinary tract cancers demonstrate microsatellite instability and loss of the mismatch repair proteins MSH2, MLH1 or MSH6 (251,1032,1507). Mutations in genes with repetitive sequences in the coding region (TGFβRII, bax, MSH3, MSH6) are found in 20-33% of cases with MSI, indicating a molecular pathway of carcinogenesis that is similar to some mismatch repair-deficient colorectal cancers. Tumours with microsatellite instabil-

Prognosis and predictive factors
The most important prognostic factor is tumour stage and for invasive tumours the depth of invasion. A potential pitfall is that, while involvement of the renal parenchyma is categorized as a pT3 tumour, some tumours that invade the muscularis (pT2) may show extension into renal tubules in a pagetoid or intra-mucosal pattern and this should not be designated as pT3. Survival for patients with pTa/pTis lesions is essentially 100%,
and patients with pT2 tumours have a survival rate of 75% (1003,1834). Survival for patients with pT3 and pT4 tumours, tumours with positive nodal disease and residual tumour after surgery is poor (1995). Other prognostic factors include patient age, type of treatment, and presence and severity of concurrent urothelial neoplasia (163,2884).

Squamous cell carcinoma

Squamous cell carcinoma is more common in the renal pelvis than in the ureter, although it is the next most common tumour after urothelial carcinoma, it is very rare in both locations. Pure squamous cell carcinomas are usually high grade and high stage tumours and frequently invade the kidney. These tumours may occur in the background of nephrolithiasis with squamous metaplasia. Survival for 5 years is rare (248).

Adenocarcinoma

Pure adenocarcinomas of the renal pelvis and ureters are rare and enteric, mucinous or signet-ring cell phenotypes, often occur concurrently. Glandular (intestinal) metaplasia, nephrolithiasis and repeated infections are predisposing factors. Most adenocarcinomas are high grade and are widely invasive at presentation (590).

Benign epithelial tumours

Urothelial papilloma and inverted papilloma

Urothelial papilloma is usually a small, delicate proliferation with a fibrovascular core lined by normal urothelium. It is extraordinarily rare and often found incidentally. Inverted papilloma is also rare being twice as common in the ureter as in the renal pelvis. Most lesions are incidentally discovered.

Villous adenoma and squamous papilloma

These benign tumours are rare in the upper urinary tract. The presence of a villous adenoma histology in a limited biopsy does not entirely exclude the possibility of adenocarcinoma and complete excision is essential.

Non-epithelial tumours of renal pelvis and ureter

Malignant tumours

The most frequent malignant stromal tumour of the ureter is leiomyosarcoma. Other malignant tumours reported are rhabdomyosarcoma, osteosarcoma, fibrosarcoma, angiosarcoma, malignant schwannoma, and Ewing sarcoma (416, 506,657,746,1745,1925,2634).

Benign tumours

Fibroepithelial polyps are exophytic intraluminal masses of vascular connective tissue and varying amounts of inflammatory cells, covered by normal transitional epithelium. These are most frequently seen in the proximal ureter in young male adults and, in contrast to urethral polyps, children are rarely affected (2828). Renal pelvic and ureteric leiomyoma, neurofibroma, fibrous histiocytoma, haemangiomia, and periureteric lipoma, including hibernoma, have been reported (91,974,1456,2449,2573,2712,2870).

Miscellaneous tumours

Neuroendocrine tumours

Few cases of ureteric phaeochromocytoma have been reported (128). Pelvic and ureteric carcinoid is similarly rare (45,1217,2260) and must be differentiated from metastatic disease (231). Carcinoids also occur in ureteroileal conduits (1343). Small cell carcinoma of the renal pelvis is confined to elderly patients (971,1347). These aggressive tumours usually contain foci of urothelial carcinoma (971,1321,1326) and have a typical neuroendocrine immunohistochemical profile (971,1326,1347).

Lymphoma

Renal pelvic and ureteric lymphomas are usually associated with systemic disease (200,331,2635), while localized pelvic plasmacytoma has been reported (1165).

Other

Rare cases of sarcomatoid carcinoma of the pelvis and ureter can show either homologous or heterologous stromal elements (621,774,2727,2882). The tumours may be associated with urothelial carcinoma in situ (2727,2882) and have a poor prognosis (621,774,2882). Wilms tumour confined to the renal pelvis or extending into the ureter (1114) and cases of malignant melanoma and choriodocarcinoma of the renal pelvis have been described (669,800,2680).
Tumours of the urethra

Definition
Epithelial and non-epithelial neoplasms of the male and female urethra, frequently associated with chronic HPV infection.

Introduction and epidemiology
Epithelial tumours of the urethra are distinctly rare but, when encountered, are usually malignant and perhaps unique among genitourinary malignancies, as they are three to four times more common in women than in men [85,920, 1799,2318]. Urethral carcinomas occurring in men are strikingly different in clinical and pathologic features when compared to tumours in women. The dissimilarities may chiefly be attributable to the distinct differences in the anatomy and histology of the urethra in the two sexes. Benign epithelial tumours are exquisitely rare in the urethra of either sex.

Etiology
Human papilloma virus plays a crucial role in the etiology of condyloma of the urethra. Congenital diverticulum as well as acquired strictures of the female urethra, contribute to female preponderance of carcinomas. Columnar and mucinous adenocarcinoma are thought to arise from glandular metaplasia, whereas cribiform adenocarcinoma showed positive PSA staining indicating origin from prostate (male or female) [1837]. Villous adenoma has been shown to occur associated with tubulovillous adenoma and adenocarcinoma of the rectum [1782]. Leiomyoma may show expression of estrogen receptors and is related to endocrine growth stimulation during pregnancy [72]. Leiomyoma may occur as a part of diffuse leiomyomatosis syndrome (esophageal and rectal leiomyomata).

Molecular pathology
Squamous cell carcinoma of the urethra is associated with HPV infection in female and male patients. High risk HPV 16 or 18 was detected in 60% of urethral carcinomas in women [2822].
Tumours of the urethra

In men, approximately 30% of squamous cell carcinomas tested positive for HPV16 (529,2821). All tumours were located in the pendulous part of the urethra whereas tumours in the bulbar urethra were negative. HPV16-positive tumours had a more favourable prognosis (2821). There is no convincing evidence for an association of urothelial carcinoma with HPV, both in the urethra and the urinary bladder. One squamous cell carcinoma of the urethra was investigated cytogenetically and showed a complex karyotype with alterations at chromosomes 2,3,4,6,7,8,11,20 and Y, but not at chromosomes 9 and 17 (732).

Epithelial tumours of the urethra

Female urethra

Malignant tumours

Macroscopy

Tumours may develop anywhere from urinary bladder to external vaginal orifice including accessory glands (Cowper and Littre glands as well as Skene glands in the female). Tumours involving the distal urethra and meatus are most common and appear as exophytic nodular, infiltrative or papillary lesions with frequent ulceration. Tumours involving the proximal urethra that are urothelial in differentiation exhibit the macroscopic diversity of bladder neoplasia: papillary excrescences (non-invasive tumour); erythema and ulceration (carcinoma in situ); and papillary, nodular, ulcerative or infiltrative (carcinoma with and without invasion). Adenocarcinomas are often large infiltrative or expansile neoplasms with a variable surface exophytic component and mucinous, gelatinous or cystic consistency. Carcinomas may occur within preexisting diverticuli.

Tumour staging

There is a separate TNM staging system for tumours of the urethra (944,2662).

Histopathology

The histopathology of female urethral carcinomas corresponds to the location. Distal urethral and meatus tumours are squamous cell carcinomas (70%), and tumours of the proximal urethra are urothelial carcinomas (20%) or adenocarcinomas (10%) (85,2532).

Squamous cell carcinomas of the urethra span the range from well differentiated (including the rare verrucous carcinoma histology) to moderately differentiated (most common) to poorly differentiated. Urothelial neoplasms may be non-invasive, papillary (neoplasms of low malignant potential, low grade and high grade carcinomas), carcinoma in situ (CIS) or invasive. CIS may involve suburethral glands, focally or extensively mimicking invasion. Invasive carcinomas are usually high grade, with or without papillary component, and are characterized by irregular nests, sheets or cords of cells accompanied by a desmoplastic and/or inflammatory response. Tumours may exhibit variable aberrant differentiation (squamous or glandular differentiation), unusual morphology (nested, microcystic, micropapillary, clear cell or plasmacytoid), or rarely be accompanied by an undifferentiated component (small cell or sarcomatoid carcinoma).

The glandular differentiation may be broadly in the form of two patterns, clear cell adenocarcinoma (approximately 40%) and non-clear cell adenocarcinoma (approximately 60%), the latter frequently exhibiting myriad patterns that often coexist - enteric, mucinous, signet-ring cell or adenocarcinoma NOS (640,1700,1955). They are identical to primary bladder adenocarcinomas. Clear cell carcinomas are usually characterized by pattern heterogeneity within the same neoplasm and show solid, tubular, tubulocystic or papillary patterns. The cyto-
logic features vary from low grade and banal (resembling nephrogenic adenoma superficially) to high grade (more frequently). Necrosis, mitotic activity and extensive infiltrative growth are commonly observed. These tumours may arise in a urethral diverticulum or, rarely, in association with mullerianosis (1954). Relationship to nephrogenic adenoma is controversial (85).

Benign tumours
Squamous papilloma, villous adenoma and urothelial papilloma of the urethra are the only three benign epithelial neoplasms, all being rare. The latter also includes inverted papilloma. The histologic features are identical to neoplasms described in the urinary bladder and other sites.

Male urethra
Malignant tumours
Macroscopy
Tumours may occur in the penile urethra, bulbomembranous urethra or the prostatic urethra; location often determines the gross appearance and the histopathology. Tumour appearance may be ulcerative, nodular, papillary, cauliflower-like, ill defined or reflective of histologic appearance – greyish-white or pearly with necrosis (squamous cell carcinoma) or mucoid, gelatinous, or cystic (adenocarcinoma). Abscess, sinus or fistulous complication may be evident. In situ lesions may be erythematous erosions (urothelial CIS) or white and plaque-like (squamous CIS).

Tumour staging
There is a separate TNM staging system for tumours of the urethra. A separate subsection deals with urothelial carcinoma of the prostate and prostatic urethra (944,2662).

Histopathology
Approximately 75% of carcinomas are squamous cell carcinoma (usually penile and bulbomembranous urethra); the remainder are urothelial carcinomas (usually prostatic urethra and less commonly bulbomembranous and penile urethra) or adenocarcinomas (usually bulbomembranous urethra) or undifferentiated (2905). Squamous cell carcinomas are similar in histology to invasive squamous cell carcinomas at other sites. Urothelial carcinoma may involve the prostatic urethra, exhibiting the same grade and histologic spectrum described in the female urethra. It may be synchronous or metachronous to bladder neoplasia. Features unique to prostatic urethral urothelial cancers are the frequent proclivity of high grade tumours to extend into the prostatic ducts and acini in a pagetoid fashion (2662,2905). Adenocarcinomas of the male urethra usually show enteric, colloid or signet-ring cell histology, alone or in combination. Clear cell adenocarcinoma is distinctly rare (640).

Benign tumours
Tumours occurring in males are similar to those described in the female urethra.

Grading of male and female urethral cancers
Urothelial neoplasms are graded as outlined in the chapter on the urinary bladder. Adenocarcinomas and squamous cell carcinomas are usually graded as per convention for similar carcinomas in other organs - well, moderately, and poorly differentiated carcinomas using the well established criteria of degree of differentiation.

Prognostic and predictive factors
The overall prognosis is relatively poor. Tumour stage and location are important prognostic factors. In females and males, proximal tumours have better overall survival than distal tumours (51% for proximal versus 6% for distal). In both sexes, or entire tumours in females (920, 1487), and 50% for proximal and 20% 5-year survival for distal tumours in males (1118,2154,2155). In both sexes, high pT tumour stage and the presence of lymph node metastasis are adverse prognostic parameters (543,865,1736). The prognosis for clear cell adenocarcinoma may not be as unfavourable as initially proposed (543,1700).

Differential diagnosis
Nephrogenic adenoma
Nephrogenic adenoma of the urethra is similar to that found elsewhere in the urinary tract. In females it is more frequently associated with urethral diverticulum and has also been noted after urethral reconstruction of hypospadias using bladder mucosa (2801,2890).

Fibroepithelial and prostatic polyps
Fibroepithelial polyps occur in both adults and children and are more common in the proximal urethra in males and the distal urethra in females (485,565). Prostatic polyps may cause hematuria but do not recur following resection. These polyps are covered by urothelial and/or prostatic epithelium and have a

Fig. 2.100 Clear cell adenocarcinoma of urethra. This tumour demonstrates a papillary architecture in which cells have clear cytoplasm and a high nuclear grade.
prominent basal epithelial cell layer (2453,2549,2770).

**Condyloma acuminatum and caruncle**

Urethral condylomas are flat or polypoid and are not always associated with external genital disease (583,795). Caruncles are inflammatory polyps of the female urethra and must be distinguished from exophytic inflammatory pseudotumour, urothelial carcinoma or metastatic tumour (127,1557,2903).

**Non-epithelial tumours of the urethra**

**Malignant tumours**

Malignant melanoma has been described in the male and female urethra. In male, the distal urethra is the most common site. Amelanotic melanoma may mimic urethral carcinoma (2130). Other reported non-epithelial tumours are *primary non-Hodgkin lymphoma* (127,1325) and *sarcomatoid carcinoma* (1352,2160). Lymphoma or sarcomatoid carcinoma has to be differentiated from atypical stromal cells described in urethral caruncles with pseudoneoplastic histology (2897).

**Benign tumours**

Leiomyoma shows immunohistochemically positive staining for vimentin, desmin and actin (72). Periurethral leiomyoma has been described associated with esophageal and rectal leiomyomatosis (969). Leiomyoma is more frequent in female urethra, but has been described also in the male (1740). *Haemangioma* occurs in the bulbar (2020) or prostatic urethra (825). *Localized plasmacytoma* has been shown to be treated by excisional biopsy (1473).

**Tumours of accessory glands**

Bulbourethral gland carcinomas may show a mucinous, papillary, adenoid cystic, acinar or tubular architecture, while rare mucinous and papillary adenocarcinomas of the paraurethral glands have been reported (301,1292,2414, 2440). Female periurethral gland adenocarcinomas are clear cell, mucinous or, rarely, prostatic (2466).