Pathology of tumours of the kidney and urinary tract

Jonathan M Salmond

Abstract

The urinary tract encompasses the kidney and the urinary collecting system, ureter, bladder and urethra. Benign lesions of the kidney include angiomyolipoma and renal oncocytoma. The main subtypes of renal cell carcinoma include clear cell, papillary and chromophobe variants. Prognostic factors reported by pathologists are reviewed, including the current grading and staging systems. Urothelial tumours include urothelial carcinoma in situ, papillary urothelial carcinoma and invasive urothelial carcinoma. Aspects of their grading and staging are covered, and several less common variants and benign urothelial lesions are mentioned. General aspects of core biopsy and resection specimens for renal disease are examined, including indications for frozen section examination.

Keywords Bladder; carcinoma; kidney; pathology; urinary tract; urothelial

Introduction

Tumours of the kidney and urinary tract represent an interesting and diverse group of lesions, as well as a significant burden of disease. Diagnostic histopathologists have a vital role to play in their accurate diagnosis and classification, in order to inform management decisions and give patients the best possible information about prognosis. The aim of this review is to describe some of the most common tumours of the renal parenchyma and the urothelial lined structures, to give trainee surgeons a useful working knowledge of the main entities encountered and to aid interpretation of pathology reports.

Tumours of the kidney

Renal biopsy specimens: Historically, percutaneous biopsy of renal tumours was avoided due to fear of tumour seeding along the biopsy tract. However, renal mass biopsy has been shown to be safe and clinically useful, particularly in the assessment of small renal masses.[1] The diagnostic rate of CT-guided renal mass biopsy has been shown to be in the region of 80–90%, and this technique has a superior diagnostic accuracy to fine needle aspiration cytology. As well as being useful in confirming the diagnosis and classification of malignant tumours, renal core biopsy can detect benign lesions such as renal oncocytoma and angiomyolipoma. In the case of malignant disease, a core biopsy can identify unusual nonepithelial neoplasms, such as lymphoma or metastatic carcinoma from a non-renal site. Finally, a core biopsy can provide a tissue diagnosis of clear cell renal cell carcinoma (RCC) in patients with metastatic disease from the kidney, permitting the use of appropriate systemic anticancer therapy, including tyrosine kinase inhibitor drugs.[2]

It is important to note that a biopsy finding of 'normal renal parenchyma', or of scarring will often represent a false-negative result, and repeat biopsy may be indicated in this situation. Although it is usually possible to determine tumour subtype on core biopsy, the histological grade is often underestimated, due to sampling error.[3]

Resection specimens: Histopathologists deal with partial nephrectomy specimens and radical resections for renal tumours. In both instances, the specimens are reported according to published guidelines, for example those of the UK Royal College of Pathologists.[4] Partial nephrectomy specimens are increasingly encountered for small renal masses. Radical nephrectomy is performed for renal cell carcinoma, while nephro-ureterectomy is performed for urothelial carcinoma of the renal collecting system and ureter.

Resection specimens are carefully examined macroscopically by the pathologist, to assess the tumour size and extent of local spread. The presence of renal vein invasion is a primarily macroscopic observation which if present denotes at least pT3 disease. Blocks of tissue from the tumour and adjacent structures are processed for histology in order to allow the tumour to be staged according to TNM criteria, and sufficient sampling of the tumour must be undertaken to allow the tumour type, grade and the presence of any other risk factors to be assessed.

Frozen section in urinary tract tumours: Frozen section examination is occasionally requested to examine surgical margins in partial nephrectomy specimens. However, these can be difficult to interpret histologically and are prone to sampling error, hence their clinical utility is debated.[5] Frozen sections are also occasionally taken to examine ureteric and urethral margins during radical cystectomy procedures for bladder cancer. Again, these are of uncertain clinical utility.[6] Perhaps the main indication for frozen section examination in urinary tract tumours is to confirm the presence of inoperable tumour in patients with an unexpected intraoperative finding of advanced disease.

Benign renal tumours

Renal oncocytoma: The classical macroscopic appearance of renal oncocytoma is of a solid lesion with a mahogany brown cut section and a central stellate scar. Oncocytomas are commonly multifocal. Most are sporadic and they occur roughly twice as commonly in men than in women. Microscopically, they comprise nests and sheets of cells with eosinophilic (pink on an H&E stain) cytoplasm. The tumour cell nuclei are bland and mitotic figures scarce (Figure 1).

Renal oncocytomas are sometimes difficult to diagnose with confidence, since their histology can closely mimic that of chromophobe RCC. The distinction largely rests on careful assessment of the morphology, augmented by immunohistochemistry. Molecular studies can be of assistance, since renal oncocytomas lack the multiple chromosomal losses generally described in chromophobe carcinoma.[7]

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Papillary adenomas are small (by definition ≤15 mm) lesions without metastatic potential, which are common incidental findings, being found at autopsy in up to 40% of patients over the age of 70. Macroscopically, they are well circumscribed pale nodules, usually present just below the capsule. The histology of papillary adenoma closely resembles that of papillary RCC type I (described below), being composed of papillary structures covered by cells with a low nuclear grade. Of note, both entities show similar genetic abnormalities, particularly loss of the Y chromosome, and trisomy of chromosomes 7 and 17, supporting the status of papillary adenoma as a precursor lesion of papillary RCC.

Angiomyolipoma: These are mesenchymal tumours which are composed of variable proportions of fat, thick walled blood vessels and smooth muscle cells. They can occur sporadically, or in patients with tuberous sclerosis. They are benign, although renal failure can occur in individuals with multiple tumours in context of tuberous sclerosis. Immunohistochemistry can be extremely helpful in confirming the diagnosis on core biopsy samples, as the smooth muscle cells often show positivity for melanocytic as well as myogenic markers.

Malignant renal tumours

Most renal tumours are renal cell carcinomas, of which clear cell RCC is the most common. Other tumour types include papillary RCC and chromophobe RCC. Collecting duct carcinoma shows some histological similarities to invasive urothelial carcinoma, and tends to show an aggressive clinical course. Other less common types of renal cancer include medullary carcinoma, mucinous tubular and spindle cell carcinoma and MIT family translocation renal cell carcinomas. Many of the renal cancer subtypes have been shown to display distinctive genetic abnormalities, which may have a bearing on their clinical course. Furthermore, renal cancer can occur in context of several recognized genetic syndromes, principally Birt-Hogg-Dube syndrome, Von Hippel-Lindau syndrome, hereditary leiomyomatosis and renal cell cancer and hereditary papillary renal cell carcinoma (HLRCC). Cigarette smoking and obesity are recognized risk factors for renal cell carcinoma. Patients on long term renal dialysis are also at increased risk.

Urothelial carcinomas account for the majority of tumours of the renal pelvis and ureter, these being histologically identical to those occurring in the urinary bladder. Occasional cases of squamous cell carcinoma and adenocarcinoma also occur at these sites.

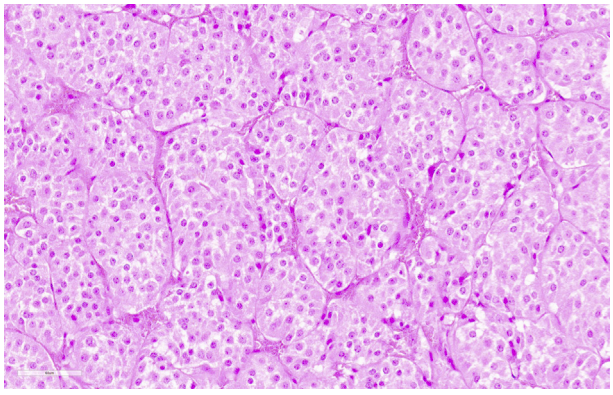

Figure 1 Renal oncocytoma, comprising nests of cells with round, cytologically bland nuclei and eosinophilic cytoplasm.

Clear cell RCC accounts for approximately 70% of cases of renal cell carcinoma. They are usually solitary, although multifocal cases can occur in hereditary syndromes, including Von Hippel-Lindau syndrome.

Common metastatic sites include lung, liver, soft tissues, adrenal gland and brain. Clear cell RCC can metastasize many years after therapy, sometimes at obscure sites.

These tumours often have a distinctive golden yellow colour macroscopically, reflecting the rich lipid content of the tumour cells, and also often contain areas of haemorrhage. They have a propensity to invade the renal sinus structures, renal vein tributaries and lymph nodes.

Microscopically, many will comprise nests of cells with a distinctive clear cytoplasm and a prominent network of thin walled blood vessels (Figure 2). Some examples of clear cell RCC fail to show typical clear cytoplasm, instead having eosinophilic (pink staining on H&E) cytoplasm.

The vast majority of sporadic clear cell RCCs show characteristic cytogenetic abnormalities involving chromosome 3p deletions. VHL gene mutations have also been demonstrated in approximately 50% of cases.

Papillary RCC accounts for approximately 10% of renal cell carcinomas. The vast majority are sporadic, although hereditary cases do occur. Macroscopically, they are often friable and necrotic with cystic degeneration. Microscopically, papillary RCC demonstrates a characteristic papillary growth pattern, with tumour cells covering branched fronds with vascular connective tissue cores. Type I papillary RCC shows cells with a modest amount of variation in size and shape. Foamy macrophages can be seen within the papillary cores (Figure 3). Type II tumours show a greater degree of cytological atypia, with multilayering of tumour cells and more abundant eosinophilic cytoplasm. Type I tumours show a greater 5 year survival than type II tumours. Papillary RCC shows a range of genetic changes, including trisomies of chromosome 7 and 17 and loss of the Y chromosome.

Chromophobe carcinoma: This variant of renal cell carcinoma tends to have a more indolent clinical course than clear cell RCC. Those tumours showing classic histology have cells with wrinkled nuclear outlines ('raisinoid' nuclei), with clearing of the immediately surrounding cytoplasm (perinuclear halos). The cell borders are distinct, said to give a plant cell like appearance. Other examples have eosinophilic cytoplasm, which can cause them to mimic renal oncocytoma histologically, a particular problem in small biopsy samples. Genetically, chromophobe carcinomas are characterized by multiple chromosomal losses, and this can be of assistance in diagnosing those cases that mimic oncocytoma on light microscopy.

Prognostic factors in renal cell carcinoma: Staging according to TNM criteria can be accomplished on examination of nephrectomy specimens, and gives important prognostic information (Table 1). Apart from pathological stage, several other prognostic factors can be identified by the histopathologist, and these have

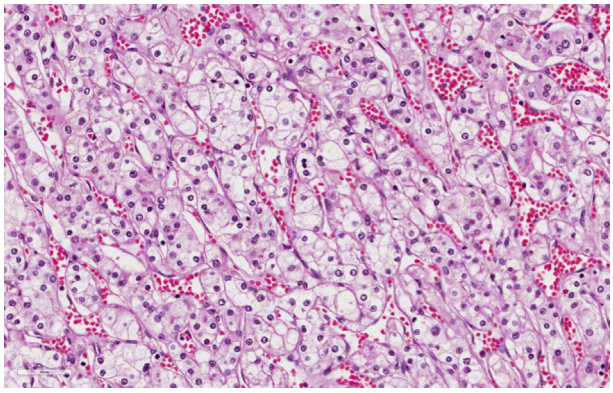

Figure 2 Clear cell renal cell carcinoma composed of a clear cells arranged in a solid architecture with a rich capillary blood supply.

been incorporated into various prognostic algorithms, such as that published by Leibovich.[8]

Grade – the best known grading system for renal cell carcinoma is the Fuhrman system. This four tier system (grades 1–4) relies upon assessment of a number of cellular features, including tumour cell nucleoli, cell size and the degree of nuclear membrane irregularity. However, the assessment of the presence of tumour cell nucleoli has been found to be most reproducible and correlates best with patient outcome. A modification of the scheme was therefore recommended by the International Society of Urological Pathology (ISUP), referred to as the ISUP grading system, also comprising four grades.[9] It should be noted that the ISUP grading scheme applies to clear cell and papillary subtypes of RCC only.

Other negative prognostic factors in RCC – a range of RCC subtypes can show areas of dedifferentiation into spindle cell sarcoma or rhabdoid change, whereby the tumour cells resemble immature skeletal muscle cells. These, together with tumour necrosis, are negative prognostic indicators.

Urinary tract tumours

The urinary tract (including the collecting system of the kidneys, ureters, bladder and most of the urethra) is lined by urothelium (otherwise known as transitional mucosa). The distal most portion of the urethra is lined by stratified squamous epithelium.

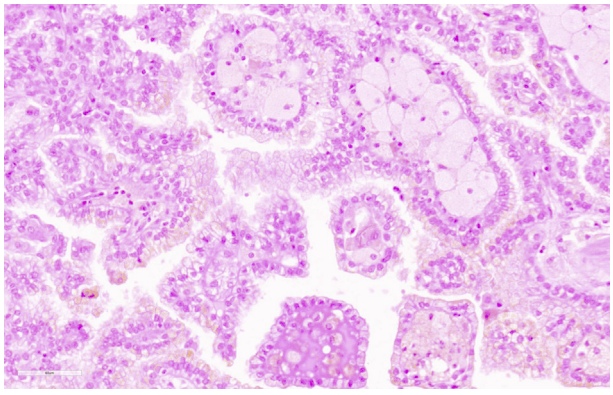

Figure 3 Papillary RCC, showing a papillary architecture and foamy macrophages in the tissue cores.

Staging of renal cell carcinoma (UICC TNM 8th Edition)

pT1	Tumor ≤7 cm in greatest dimension, limited to the kidney
pT1a	Tumor ≤4 cm in greatest dimension
pT1b	Tumor >4 cm but ≤7 cm in greatest dimension
pT2	Tumor >7 cm in greatest dimension, limited to the kidney
pT2a	Tumor >7 cm but ≤10 cm
pT2b	Tumor >10 cm
pT3	Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland
pT3a	Tumor grossly extends into the renal vein or tumor invades perirenal and/or renal sinus fat
pT3b	Tumor grossly extends into the vena cava below the diaphragm
pT3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
pT4	Tumor invades beyond the Gerota fascia (including direct extension into the ipsilateral adrenal gland)

Table 1

The majority of tumours arising in urothelium occur within the urinary bladder. Bladder cancer is the seventh most common cause of cancer death in the UK, accounting for approximately 5000 deaths per annum.[10]

Most tumours occurring within the renal collecting system, ureters, bladder and urethra are flat, papillary or invasive urothelial carcinomas, with lesser proportions of squamous neoplasms, adenocarcinoma and other unusual tumour types. The terms 'transitional cell carcinoma' and 'urothelial carcinoma' are synonymous.

Bladder cancer occurs two to five times more commonly in men than in women. Most are sporadic. Tobacco smoking is the most significant single risk factor for the development of bladder cancer, although other recognized risk factors include occupational exposure to carcinogens (including aniline dyes and aromatic amines). There may be a long latency period between exposure to the carcinogen and the development of neoplasia.[11] Urothelial tumours tend to be multifocal, and carcinoma in situ is often found in biopsies of mucosa separate to invasive urothelial carcinoma.

Grading systems for urothelial neoplasms

The WHO 1973 classification of transitional cell carcinoma uses three grades. Grade 1 tumours have the least degree of cellular atypia compatible with malignancy, while grade 3 tumours have the greatest degree of atypia.

The 1973 scheme is well validated. However, this system has been subject to criticism due to the relatively poorly defined histological grading criteria. This led to the rather unsatisfactory practice of tumours being described as being grade '1/2' or '2/3'.[12] In general application, the large proportion of cases assigned to the grade 2 category represents a heterogeneous group, with some lesions behaving more akin to grade 3 lesions, while others showing a more indolent behaviour, similar to grade 1 lesions.

Subsequent revisions of the WHO scheme aimed to improve interobserver agreement by providing more precise criteria for assigning grade. In 1998, the ISUP proposed a new grading system which was adopted in large measure by the WHO in 2004.

The classification was updated in 2016, although the grading criteria for urothelial carcinoma were not altered.[12]

Rather than using a three-tier grading system, under the 2016 scheme urothelial carcinomas are classified as being low or high grade. A new category 'papillary urothelial neoplasm of low malignant potential' (PUNLMP) has been introduced to encompass those lesions which show the least degree of atypia, in order to avoid labelling patients with a cancer diagnosis for a relatively indolent non-invasive lesion. Nonetheless, lesions classified as PUNLMP do still have a significant risk of progression, and warrant follow-up.

A potential source of confusion is that there is not a direct correlation between the 1973 and 2016 grades. While all 1973 grade 3 lesions are high grade, grade 2 lesions under the 1973 scheme are split between low and high grade according to the 2016 system. Grade 1 lesions under the 1973 scheme are split between PUNLMP and low grade papillary urothelial carcinoma under the 2016 system (Table 2).

WHO classification of urothelial neoplasms: The most common entities within the current WHO classification of urothelial neoplasms are summarized below.

Urothelial papilloma – are rare benign tumours, accounting for under 1% of papillary urothelial neoplasms. Most are solitary, and show a similar cystoscopic appearance to low grade papillary urothelial carcinoma. The histological criteria for diagnosis are strict. Morphologically, they comprise delicate fibrovascular cores, covered by otherwise completely normal urothelium, showing no epithelial thickening or cytological atypia.

Inverted papilloma – like urothelial papilloma, these are usually solitary and comprise less than 1% of urothelial neoplasms. The trigone is the most common location. Cystoscopically, they are smooth surfaced polypoid lesions. Histologically, they comprise stands of normal urothelium invaginating into but not invading the lamina propria. The surface urothelium is normal.

Papillary urothelial neoplasm of low malignant potential (PUNLMP)

As mentioned, these are relatively indolent tumours, with a lower risk of progression than low grade papillary urothelial carcinoma. Histologically, they comprise papillary fronds covered by epithelium showing only the mildest degree of atypia, but which is thicker than normal urothelium.

Non-invasive papillary urothelial carcinoma: These are neoplasms composed of variably atypical urothelium covering papillary fronds, without invasive growth. As already mentioned, they are graded as low or high grade, according to well defined histological criteria. For example, low grade tumours show a predominantly ordered epithelium with few mitotic figures, while high grade tumours show a predominantly disordered epithelium with frequent mitotic figures at all levels of the epithelium. High grade tumours carry a higher risk of progression than low grade tumours, and all show a tendency to recur.

Flat urothelial lesions

Urothelial dysplasia: A proportion of bladder biopsies will show mild degrees of cytological atypia which are difficult to classify. Urothelial dysplasia is defined as a flat lesion with appreciable cytologic and architectural abnormalities but that fall short of the criteria required for a diagnosis of urothelial CIS. Although urothelial dysplasia may occur in isolation, it most often occurs in the context of concurrent or previous urothelial neoplasia. Histologically, the diagnosis of urothelial dysplasia is challenging, since there is an overlap with the histological feaures seen in reactive change, for example due to inflammation or previous instrumentation.

Carcinoma in situ (CIS): Cystoscopically, urothelial CIS may be seen as flat erythematous patches, although it can be macroscopically undetectable or show only very subtle changes. It is often multifocal and carries a risk of progression to invasive urothelial carcinoma. CIS may occur de novo (primary) or be present in association with invasive urothelial carcinoma elsewhere (secondary). Histologically, CIS appears as a flat lesion in which the surface epithelium contains cytologically malignant cells (Figure 4). By definition, there is lack of invasive growth (i.e. the neoplastic cells are confined to the basement membrane). The diagnosis is primarily based on the recognition of the requisite degree of cytological atypia on an H&E section, although immunohistochemistry can provide support to the diagnosis; CIS often showing abnormal full-thickness immunostaining for the marker CK20 and p53, in contrast to normal urothelium, which tends to show only partial thickness staining. One characteristic of carcinoma in situ is that it often becomes dyscohesive, with shedding of the neoplastic cells. This can cause difficulties with histological diagnosis, in cases where there are only very few surface epithelial cells remaining for pathological assessment.

Invasive urothelial neoplasms

Infiltrating urothelial carcinoma: This is defined as a urothelial tumour which invades beyond the basement membrane. Macroscopically, invasive urothelial carcinoma can form a polypoid, exophytic mass, or be sessile and diffusely infiltrative, with or without ulceration. Unlike non-invasive papillary urothelial carcinomas, histological grade is of limited

Correlation between WHO 1973 and 2016 grading systems for urothelial carcinoma

WHO 1973	Grade 1		Grade 2	Grade 3
WHO 2016	PUNLMP	Low Grade		High Grade

Table 2

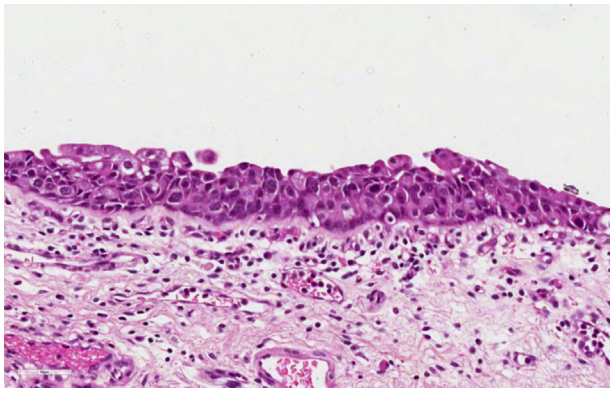

Figure 4 Urothelial carcinoma in situ, showing flat epithelium with cytologically malignant cells and abundant mitoses.

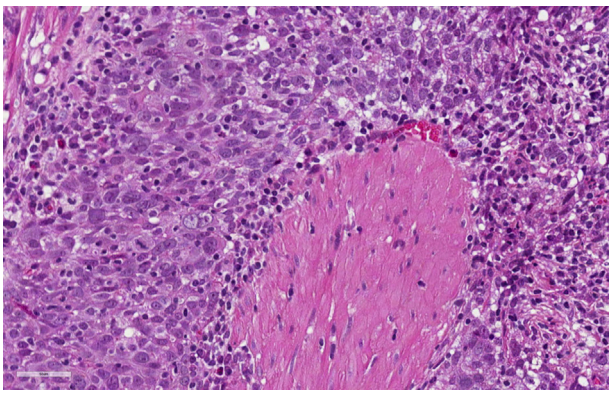

Figure 5 Infiltrating urothelial carcinoma, showing nests of tumour cells invading detrusor muscle bundles.

usefulness for prediction of outcome in invasive urothelial carcinoma, pathological stage being of much greater prognostic importance (Table 3).

Biopsy and transurethral resection (TURBT) specimens are useful in confirming the presence of invasive disease, although both have limitations. Recognition of invasion of muscularis propria (detrusor muscle) in such samples indicates a minimum of pT2 disease (Figure 5). However, the pathologist needs to take care to avoid mistaking invasion of the thin bundles of muscularis mucosae (present in the lamina propria) for muscularis propria invasion. Similarly, adipose tissue is frequently present throughout the bladder wall. Therefore, the diagnosis of extravesical fat invasion (pT3 disease) cannot be made on a TURBT specimen.

Staging should be determined in the multidisciplinary team setting, in light of all available clinical, radiological and pathological information.

Urothelial carcinoma with divergent differentiation, and other subtypes: Invasive urothelial carcinoma shows a great propensity towards divergent differentiation. Squamous differentiation is seen in approximately 20% of bladder carcinomas. Although previously thought to be a negative prognostic indicator, some doubt has been cast on this.[13] Only tumours showing pure squamous differentiation are classified as squamous carcinoma. Glandular differentiation is another well-described pattern of divergent differentiation, although the clinical significance of this finding is unclear. Small cell carcinoma of the bladder often occurs in association with more typical urothelial carcinoma, and is often locally advanced at presentation, with high rates of metastasis.

Several other subtypes of urothelial carcinoma are recognized. Some, like nested and micropapillary variants, are significant for pathologists as they can appear histologically bland on superficial biopsies, despite being widely invasive. Sarcomatoid carcinoma of bladder is a biphasic tumour comprising malignant epithelial and mesenchymal elements, the latter often taking the form of an undifferentiated spindle cell neoplasm. This finding is generally associated with a poor clinical outcome.

Staging of urothelial carcinoma of the bladder (UICC TNM, 8th Edition)

pTa	Noninvasive papillary urothelial carcinoma
pTis	Carcinoma in situ
pT1	Tumor invades subepithelial connective tissue
pT2	Tumor invades muscularis propria (detrusor)
pT2a	Tumor invades superficial muscularis propria (inner half)
pT2b	Tumor invades deep muscularis propria (outer half)
pT3	Tumor invades perivesical tissue
pT3a	Microscopic perivesical tissue invasion
pT3b	Macroscopic perivesical tissue invason (extravesical mass)
pT4	Tumor invades adjacent organs
pT4a	Tumor invades prostatic stroma, seminal vesicles, uterus, vagina
pT4b	Tumor invades pelvic wall, abdominal wall

Table 3

Squamous cell carcinoma of bladder: This term is reserved for bladder tumours showing a pure squamous morphology.[14] In most populations, squamous cell carcinoma accounts for 1–3% of all bladder tumours, being more common in females than in males. As for urothelial carcinoma, there is a strong association with tobacco smoking. In addition, there is a link between chronic irritative processes and the development of SCC of bladder, most notably schistosomiasis infection. Histologically, the tumour shows intercellular bridge formation and keratinization. Background keratinizing squamous metaplasia is common. By definition, there is no associated in situ or invasive urothelial carcinoma component.

Adenocarcinoma of bladder: Similar to squamous cell carcinoma, a purely glandular morphology is required for the diagnosis of adenocarcinoma of bladder. They can occur at the dome, in association with urachal remnants, or elsewhere in the bladder. These tumours tend to be high stage at presentation with a relatively poor prognosis.

Metastasis to the bladder: Local invasion from prostatic adenocarcinoma in men and from gynaecological tract tumours in women is well described, in addition to metastasis from carcinomas of breast and various other primary sites. These can be mistaken histologically for primary bladder carcinoma and it is important to note on the specimen request form accompanying

bladder tumour specimens if there is any history or suspicion of malignancy in adjacent organs or at another site.

Conclusion

It is hoped that this article has provided a useful summary of the principal tumour types occurring in the kidney and urinary tract. The grading and classification of urothelial neoplasms can seem confusing, particularly with the reporting of several systems in parallel, as is currently commonplace in the UK. Clinicopathological discussion, at MDT or elsewhere, can help to clarify any areas of confusion, and surgical trainees will always be welcome to visit their local pathology department to discuss cases and to broaden their knowledge. ◆

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