Upper tract urothelial cancer

Tim Lane

Abstract

Upper tract transitional cell carcinoma is a lethal disease with half the patients dead within 5 years of diagnosis. Unlike urothelial tumours arising in the bladder, the disease is more likely to be invasive at the time of diagnosis and in part reflects the poorer prognosis. It is a biologically aggressive disease with a high chance of recurrence even after local control. Diagnosis is made by a combination of upper tract imaging, urine cytology and ureteroscopic biopsy. Organ-confined disease is amenable to radical surgery, whilst superficial low-grade disease may be managed endoscopically. A number of prognostic factors have been incorporated into nomograms to predict non-organ confined disease. Even those with apparently organ-confined disease are prone to recurrence. As a result regular surveillance protocols are in place to identify both local and metastatic spread as well as metachronous bladder lesions.

Keywords Transitional cell carcinoma (TCC); upper tract

Epidemiology and aetiology

Urothelial carcinoma is the fourth most common malignancy.[1] Much has been learned about the disease from patients with bladder cancer (the majority of who have transitional cell carcinoma) with 90–95% of urothelial cancers arising in the bladder. Between 5% and 10% of urothelial cancers arise in the upper tracts (with those arising in the renal pelvis and calyces being twice as common as in the ureters). In the Western world the incidence of upper tract urothelial tumours approaches 1–2 per 100,000 of the population. Those urothelial tumours that arise in the upper tracts have a worse prognosis than those arising in the bladder (and in turn those arising in the ureters carry with them even poorer outcomes). Pyelocalyceal tumours are twice as common as common as ureteral tumours. The majority of patients presenting with upper tract disease are in their eighth and ninth decades and there is a 3:1 male: female ratio. Those individuals presenting earlier in life (less than 60 years) are likely to have a hereditary form of the disease (and there is sometimes an association with hereditary non-polyposis colorectal cancer). DNA sequencing may be required to differentiate hereditary from sporadic forms of the disease. The worse prognosis associated with upper tract tumours is in part associated with the higher rate of invasion at diagnosis (with 60% being diagnosed with invasive disease compared with 15% in those with bladder tumours).

Some of the risk factors associated with the development of upper tract transitional cell carcinomas (TCCs) are unsurprisingly, similar to those linked with bladder cancer. Smoking and a number of agents normally associated with occupational exposures are high up on the list of incriminating agents. In the case of the latter, aromatic amines used in the textile, rubber and dye industries effect changes through causative agents such as benzidine and β-naphthylamine (although such agents have been widely banned in modern industrialized countries). Many years of exposure are generally required with latency periods of up to 20 years generally seen before the development of tumours. Upper tract tumours associated with the drug phenacetin are now uncommon following the withdrawal of the drug in the 1970s. Balkan endemic nephropathy (a chronic tubulointerstitial nephritis) which classically affected residents of rural villages in the vicinity of the river Danube has a strong association with upper tract urothelial tumours. The incidence is again, however, on the decline. Agents such as aristolochic acid contained in *Aristolochia fangchi* and *Aristolochia clematis* and which cause mutations in the p53 tumour suppressor gene, have been implicated. Part of the variability in terms of patient susceptibility to these agents lies in the differential expression of activating and de-activating enzymes (the latter resulting in sulphation of the causative agents) in relation to the latter. Likewise, the exposure to arsenic has been proposed to explain the high incidence of upper tract disease in Taiwan.

Pathology

As with bladder cancer the underlying pathology is that of a urothelial carcinoma arising from transitional cells. A number of morphological variants exist and these are invariably associated with a poorer prognosis. They include micropapillary, plasmacytoid, small cell (neuroendocrine) and lymphoepithelial variants. One rare form of upper tract urothelial cancer is an epidermoid cancer. Here the development of tumour is associated with the chronic inflammation and infection associated with urolithiasis. Higher tumour grade (G1–3) is associated with poorer cancer specific survival as is the association with CIS (carcinoma-in-situ). Multi-focality, lymphovascular invasion, tumour size and tumour necrosis are also all independent markers of more aggressive disease. Tumour architecture is another important assessment and one which can only be gleaned for ureteroscopic direct visualization of tumour. In this respect a flat or sessile appearance of a urothelial tumour predicts a considerably more aggressive clinical path.

Diagnosis

Classic symptoms of upper tract urothelial carcinoma (as with bladder cancer) include visible or non-visible haematuria (70–80%). Flank pain is an additional feature of those with upper tract disease in 20–40% of patients.[2] Occasionally systemic symptoms such as anorexia, weight loss, fever, night sweats etc. may prompt the astute clinician to search for signs of metastasis.

Imaging

Computed tomography urography (CTU) has a high diagnostic accuracy for urothelial cancers (Figure 1). The majority are detected as space occupying lesions. Flat lesions are less clearly well-defined and diagnostic accuracy less assured – with inflammatory lesion and capillary haemangiomas forming part of the differential. For those with significant renal impairment

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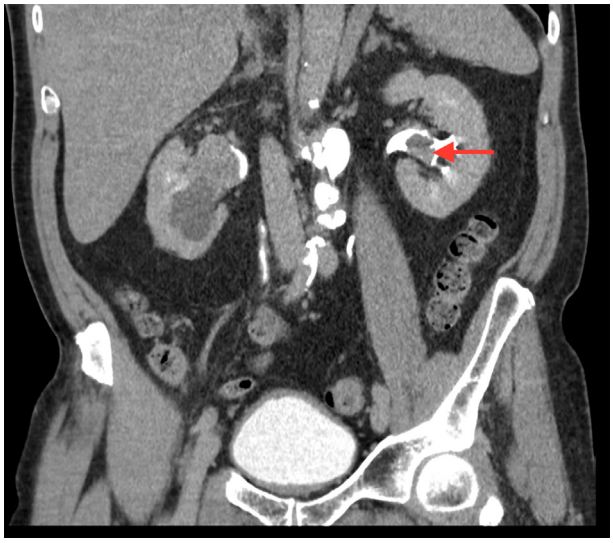

Figure 1 CT urogram of urothelial cancer.

magnetic resonance urography (MRU) represents an alternative modality. Whilst there is a reduced sensitivity and specificity it nevertheless represents a useful alternative. Even so, in those with significantly reduced renal impairment (a creatinine clearance of <30 ml/minute) gadolinium-based contrast media should be avoided because of the risk of nephrogenic systemic fibrosis. In those with ureteral lesions the presence of hydronephrosis represents a poor prognostic sign. Multiple studies have linked hydronephrosis with advanced disease, tumour metastasis and poor prognosis. It is a useful surrogate for advanced stage and poor cancer specific survival.

Urinary cytology and biomarkers

A positive urine cytology results in the absence of any bladder tumours on cystoscopy is suggestive of an upper tract urothelial lesion. In this respect a number of innovative markers such as NMP-22, BTA-stat and FISH based assays are also of utility. Where tumours are located within the renal cavity then this should ideally be acquired in-situ. Whilst none of these is diagnostic alone they form part of the diagnostic assessment, the entirety of which is used in the diagnosis of upper tract tumours.

Diagnostic ureteroscopy

Ureteroscopy and flexible ureterorenoscopy allow for upper ureteric lesions to be visualised directly and biopsied. It allows that tumour grade can be determined in over 90% of cases – with biopsies having low false negative rates. Technical developments in ureteroscopes and narrow-band imaging promise to improve the visualization and diagnosis of flat lesions.

A combination of ureteroscopic findings, histology, cytology and imaging collectively play a significant role in determining the most appropriate intervention – whether this be a radical and expirative treatment or alternatively an endoscopic management.

Staging

The current TNM classification (2009) is described in Table 1. Where tumour invades the subepithelial connective tissue (T1) the disease remains localized but where the disease becomes muscle invasive (T2) the prognosis dramatically worsens (especially where lesions are identified in the ureter). Where disease extends further beyond the muscularis into the renal parenchyma or peri-pelvic fat (renal pelvis) or peri-ureteric fat (ureter) the disease is deemed T3. Peri-pelvic or ureteric stranding may be picked up on standard contrast imaging and is a sign of this. Where tumour invades through the renal parenchyma into the peri-nephric fat or into adjacent organs the disease is staged at T4 disease.

TNM classification

T – Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
	Ta Non-invasive papillary carcinoma
	Tis Carcinoma in-situ
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T3	(Renal pelvis) Tumour invades beyond muscularis into peri-pelvic fat or renal parenchyma (Ureter) Tumour invades beyond muscularis into peri-ureteric fat
T4	Tumour invades adjacent organs or through the kidney into perinephric fat
N – Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node 2 cm or less in the greatest dimension
N2	Metastasis in a single lymph node more than 2 cm but not more than 5 cm in the greatest dimension or multiple lymph nodes, none more than 5 cm in greatest dimension
N3	Metastasis in a lymph node more than 5 cm in greatest dimension
M – Distant metastasis	
M0	No distant metastasis
Ml	Distant metastasis

Table 1

Prognosis

Unfortunately upper tract urothelial carcinomas have a poor prognosis (Figure 2). Tumour stage and grade are the single most important prognostic factors. Those with T2/T3 disease have a less than 50% 5-year survival rate and those with T4 disease less than 10%. Those tumours arising in the ureter or are multifocal carry the poorest prognosis. Flat urothelial lesions (those with a sessile growth pattern) have particularly poor outcomes. Hydronephrosis has been a feature consistently associated with poor outcomes. It appears to predict an aggressive disease pattern and an advanced pathological disease.[3] It has been independently linked with cancer metastasis and cancer specific survival. In recent years a number of tissue based molecular markers have been identified as having positive predictive prognostic value. A p53 over-expression has been identified as being associated with aggressive tumours and poor prognosis but has not necessarily emerged as an independent prognostic factor

