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, whereas 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).

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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

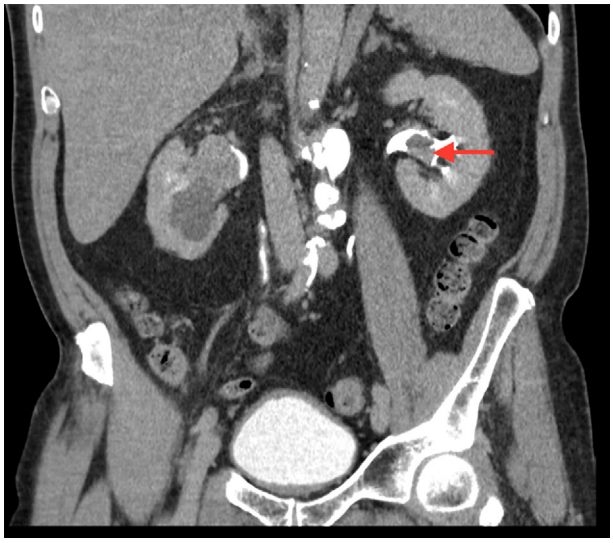

Figure 1 CT urogram of urothelial cancer.

well-defined and diagnostic accuracy less assured – with inflammatory lesion and capillary haemangiomas forming part of the differential. For those with significant renal impairment magnetic resonance urography (MRU) represents an alternative modality. While 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. While 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 visualized 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.

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

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

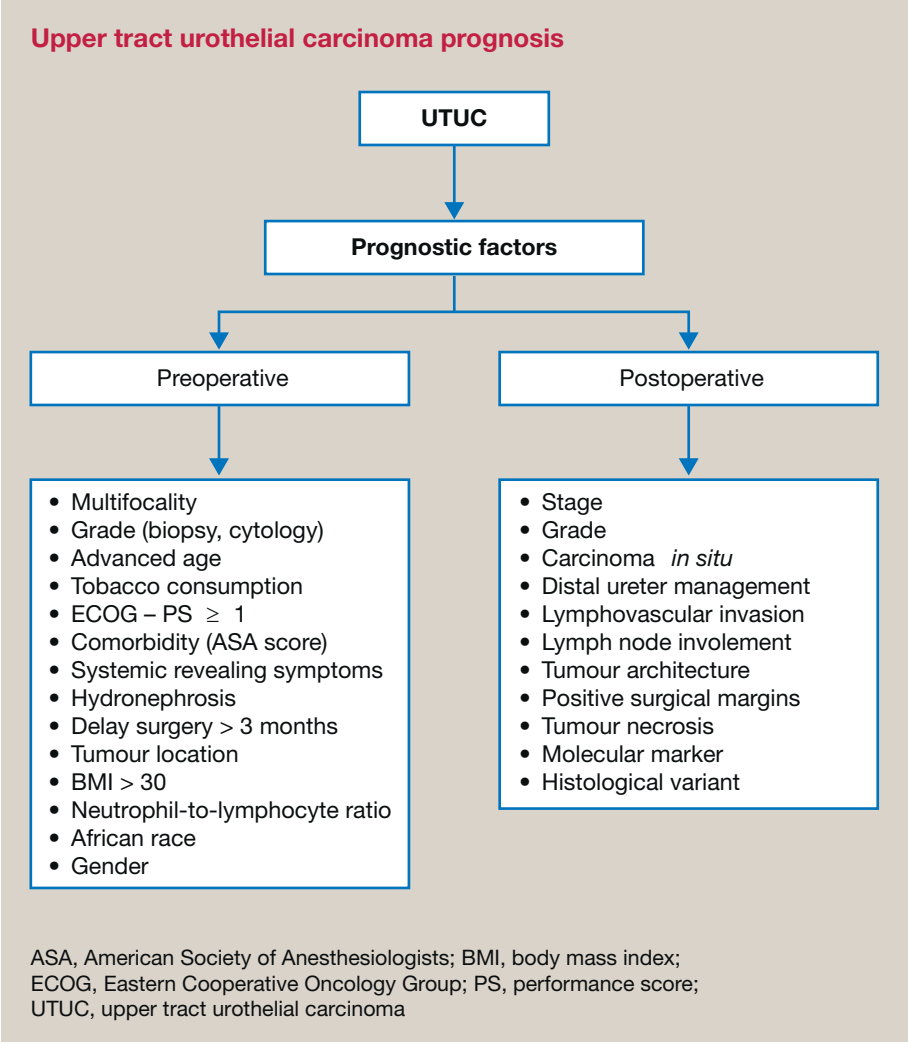

Figure 2

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 when adjusted for by other prognostic features. By contrast, the cell proliferation protein Ki-67 has been linked independently with adverse outcomes. The molecular markers EGFR, uroplakin III and Snail have also shown promise as potential markers of prognosis. The angiogenesis factor hypoxia-inducible factor 1α has also been shown to be linked with recurrence free survival and cancer specific survival. Likewise, E-cadherin and CD24 mucin-like adhesion molecule have also been shown to have independent prognostic significance. Some features can be assessed postoperatively and add additional prognostic significance. For example, lymphovascular invasion (present in 20% of upper tract lesions) is associated with negative outcomes. A positive surgical margin after radical surgery is a poor sign for cancer specific survival as is extensive tumour necrosis.

A number of nomograms have been developed to incorporate a number of these independent prognostic factors. Some have been used to predict non-organ confined disease.

Margulis, for example, developed one such nomogram to predict non-organ confined disease based on tumour grade, architecture and location. Favaretto developed a similar tool – this time to predict muscle-invasive and non-organ confined disease based on imaging and ureteroscopic findings. Their true clinical utility has however yet to be established.

Management of localized disease

In those with localized and low-risk disease there are minimally invasive kidney-sparing alternatives to the traditional radical nephro-ureterectomy (Figure 3). Where high-risk disease presents itself, more conservative approaches can also be considered where there is renal insufficiency or a solitary kidney. In low-risk cancers nephron-sparing approaches should be considered the preferred option. Endoscopic ablation has increasingly been adopted as a management tool for these patients. There are laser requirements and the need for access to flexible ureteroscopes etc., and from a patient perspective a realization that a more

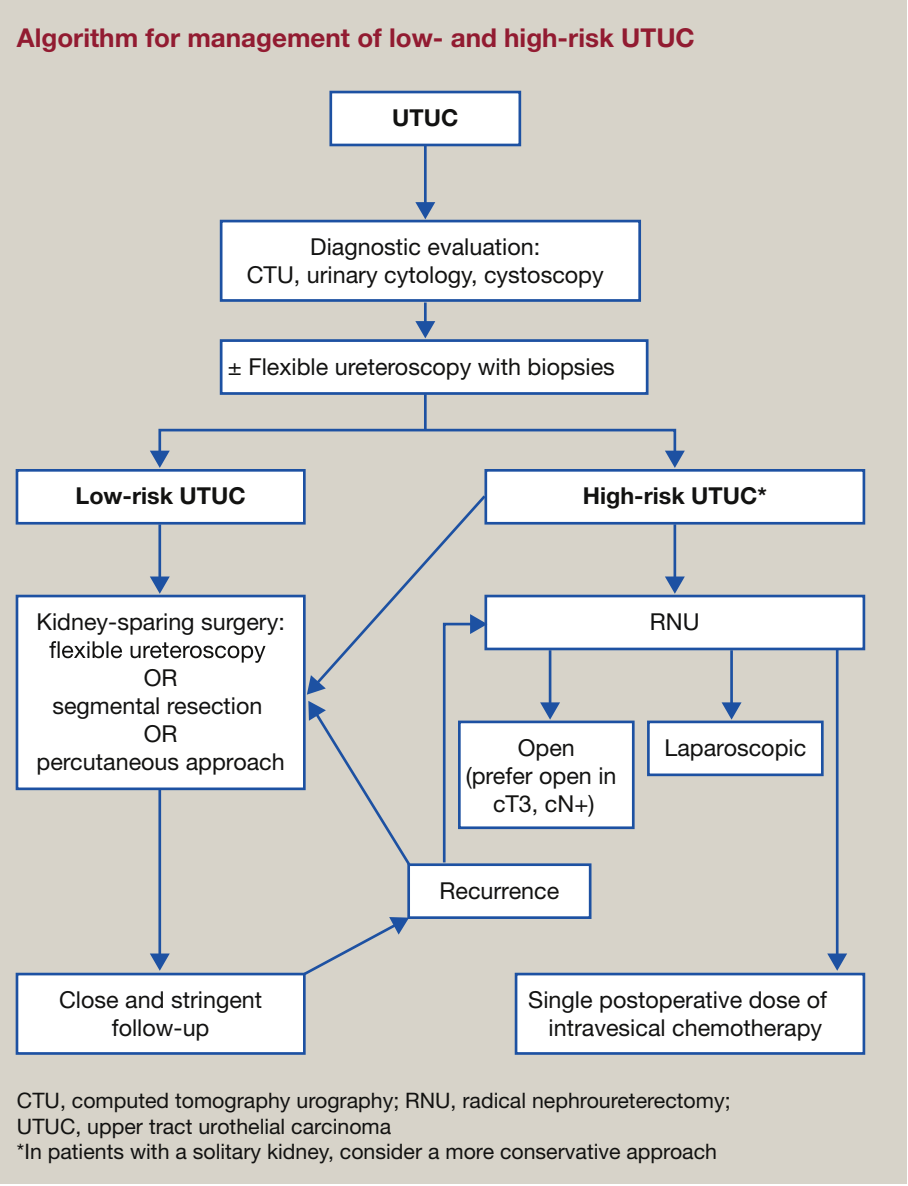

Figure 3

stringent surveillance program is necessary. There remains a very real risk of under-staging and under-grading of the disease process with endoscopic management. A variety of percutaneous approaches have also been employed to access low-grade tumours in the renal cavities (such as those arising in the lower calyceal systems) where access has been limited with flexible ureterorenoscopy. With advances in technology – particularly with the development of distal-tip deflecting scopes – the indication for percutaneous approaches is diminishing. Open surgical (and nephron-sparing) approaches to localized disease include segmental ureteric resections and distal ureterectomy and are very real options. Partial nephrectomy and partial pyelectomy are rapidly becoming historical options – with precious few indications to justify their use. The excision and re-implantation of the distal ureter to the bladder tends to be less problematic than segmental excisions of ureteric lesions at the iliac and lumbar levels. In those with CIS disease the use of BCG or mitomycin-C has previously been employed and usually via an antegrade approach. Retrograde approaches using a ureteric catheter have also been employed. The placement of a JJ-stent effectively allows for the reflux of agents instilled intravesically to be refluxed along the appropriately stented ureter. While this may allow treatment of distal ureteric lesions, it is inadequate for lesions situated in the renal pelvis or upper ureter.

Radical nephro-ureterectomy

Open radical nephro-ureterectomy with the excision of a bladder cuff remains the favoured and most reliable treatment for high-risk upper tract urothelial cancer whatever the location. While there are a number of differing surgical approaches they all aim for the same oncological outcome. Increasingly, laparoscopic approaches are employed to this effect. Oncological outcomes are at least as good, with the added advantages of less blood loss and

shorter recovery times. Large tumours or invasive disease is less amenable to a laparoscopic approach and would favour a more standard open approach. Open procedures would appear to provide better oncological outcomes in such cases. The role of a lymph node dissection is far from clear. It would certainly not appear to offer any survival benefit for those with low-grade superficial disease given the reported incidence of lymph node involvement in such cases is low (2.2% in T1 disease). The rate of lymph node involvement increases with increazing stage. That said the evidence for lymph node resections in even these cases still remains to be determined. Recurrence of urothelial cancer within the bladder following surgery is well recognized. A single intravesical postoperative instillation of mitomycin-C immediately following surgery has been shown to reduce the recurrence rate within the bladder for almost one year.

Management of advanced disease

In patients with metastatic disease there is no role for surgery other than in a palliative capacity.[4] The role of systemic chemotherapy is unclear. While there are some studies which might suggest some advantages to cisplatin-based adjuvant therapies, there is currently insufficient evidence to recommend it as a treatment. The role of radiotherapy is similarly unclear but it is likely only to have an impact on local recurrence only. Neither chemotherapy nor radiotherapy currently offers a survival advantage. Their role is principally in the palliative setting.

Surveillance

Surveillance regimes depend largely as to whether or not radical or more conservative approaches have been undertaken as primary treatment. For those having undergone radical nephro-ureterectomy follow-up arrangements change over time in keeping with the relative risk of recurrence. Certainly, a close follow-up is required to identify metachronous bladder lesions as well as local and distant recurrences. While local recurrence following radical nephro-ureterectomy is unusual, distant metastases do occur and the risk of this appears related to those prognostic features outlined previously.

For those presenting with non-invasive disease. 3-monthly cystoscopies and urine cytology assessments are undertaken for a year and then annually for at least 5 years. CT urography is undertaken yearly. For invasive tumours CT urography is undertaken more frequently with bi-annual CT scans for 2 years and annually thereafter. The recommendations for the surveillance of those undergoing kidney conserving surgery are more individualized. Cystoscopy, ureteroscopy and in-situ cytological assessments are made at three and six months, six-monthly for two years and then annually thereafter. CT urography is undertaken at 3 and 6 months and then annually thereafter. ◆

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