European Journal of Radiology 98 (2018) 50–60

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Review

Upper tract urothelial cancer

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ARTICLE INFO

Keywords:
CTU
MRU
Urothelial carcinoma imaging

ABSTRACT

While urothelial carcinoma is a very common tumor, involvement of the upper tract is relatively uncommon. Consequently, there are no consensus imaging recommendations for upper tract disease. CT urography is the dominant imaging modality for the upper tract, but despite its excellent performance characteristics and being widely accepted as standard of care there is great variability in how CTU exams are performed across practices. MR urography has limited current application, but has the potential to become more mainstream in the future with continued technical advances. Upper tract urothelial carcinoma can manifest as a variety of appearances: a papillary lesion, focal wall thickening, focal enhancement, or as an infiltrative lesion. Pelvicalyceal location is about twice as common as in the ureter. Tumors in the pelvicalyceal location often manifest as an irregular enhancing soft tissue attenuation filling defect, and may be sessile or polypoid in morphology. Within the ureter, 73% are located in the distal segment.

1. Upper tract urothelial carcinoma – clinical background

1.1. Epidemiology

Urothelial carcinoma (UC) is the 4th most common tumor. The cost per patient for a diagnosis of urothelial carcinoma is the highest of all malignancies, due to frequent procedures for monitoring and treatment [1]. 90–95% of UC occurs as urothelial carcinoma of the bladder (UCB), with upper tract urothelial carcinoma (UTUC) accounting for 5–10%. As it has often been grouped with other renal cancers, the true incidence of UTUC is not precisely known. Estimates suggest that approximately 15% of renal tumors are UC [2]. Pelvicalyceal location is twice as common for UTUC as ureteral location [3]. The incidence of UTUC has been increasing recently, possibly related to improving survival of patients with UCB and the associated risk of developing synchronous UTUC in those patients [2]. Concurrent UCB occurs in 17% of patients with UTUC [4]. Notably, 60% of UTUCs are invasive at diagnosis, compared to only 15–25% for UCBs [5]. UTUC is approximately twice as common in men, a less marked gender disparity as that seen with UCB [6].

Approximately 75% of UTUC presents with hematuria (gross or microscopic) [7], much less commonly due to flank pain or palpable mass. The dominant risk factors mirror UCB: tobacco, occupational exposure to aromatic amines, analgesics particularly phenacetin (but that etiology has greatly declined since banning in 1970s), and aristolochic acid. The incidence is particularly high in Taiwan, and there are some known genetic predispositions such a Lynch syndrome, and Balkan nephropathy which carries up to a 200× risk of UTUC [8]. Some patients with micro-satellite instability mutations more commonly develop UTUC and rarely UCB [9].

1.2. Staging and prognosis

The World Health Organization (WHO) classification for UC was revised last in 2004. Tumor pathologic T staging is similar to that of UCB (Fig. 1). UTUC spreads most commonly by direct invasion/extension and via lymphatics. The ureteral wall is much thinner than the thicker muscular bladder wall, which may account for more aggressive behavior of UTUC. Although lymph node size impacts N classification, laterality does not. Sites of regional lymph node involvement, if present, depend on the level of the upper tract tumor with renal pelvic and proximal ureteral tumors more likely to spread to renal hilar, paracaval, retrocaval, and paraaortic nodes whereas distal ureteral tumors drain to common iliac and other pelvic nodal stations. Hematogenous spread is less common, but UC spreads hematogenously to liver and bones.

There are many prognostic factors for UTUC, with varying degrees of impact, too exhaustive to detail. In general, tumor stage, tumor size, multifocality, and histologic grade have the greatest impact on prognosis. Tumor grading shows lesser difference in prognostication of outcome compared to tumor stage, with stage being the single most important prognostic factor for UTUC (Table 1) [10,11]. Muscle invasive tumor has a very poor prognosis, with 5 year survival less than 50% for stage pT2/pT3, and < 10% for pT4. [12] Of particular note, presence and severity of ipsilateral hydronephrosis on pre-operative

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http://dx.doi.org/10.1016/j.ejrad.2017.10.021
Received 1 September 2017; Received in revised form 21 October 2017; Accepted 23 October 2017

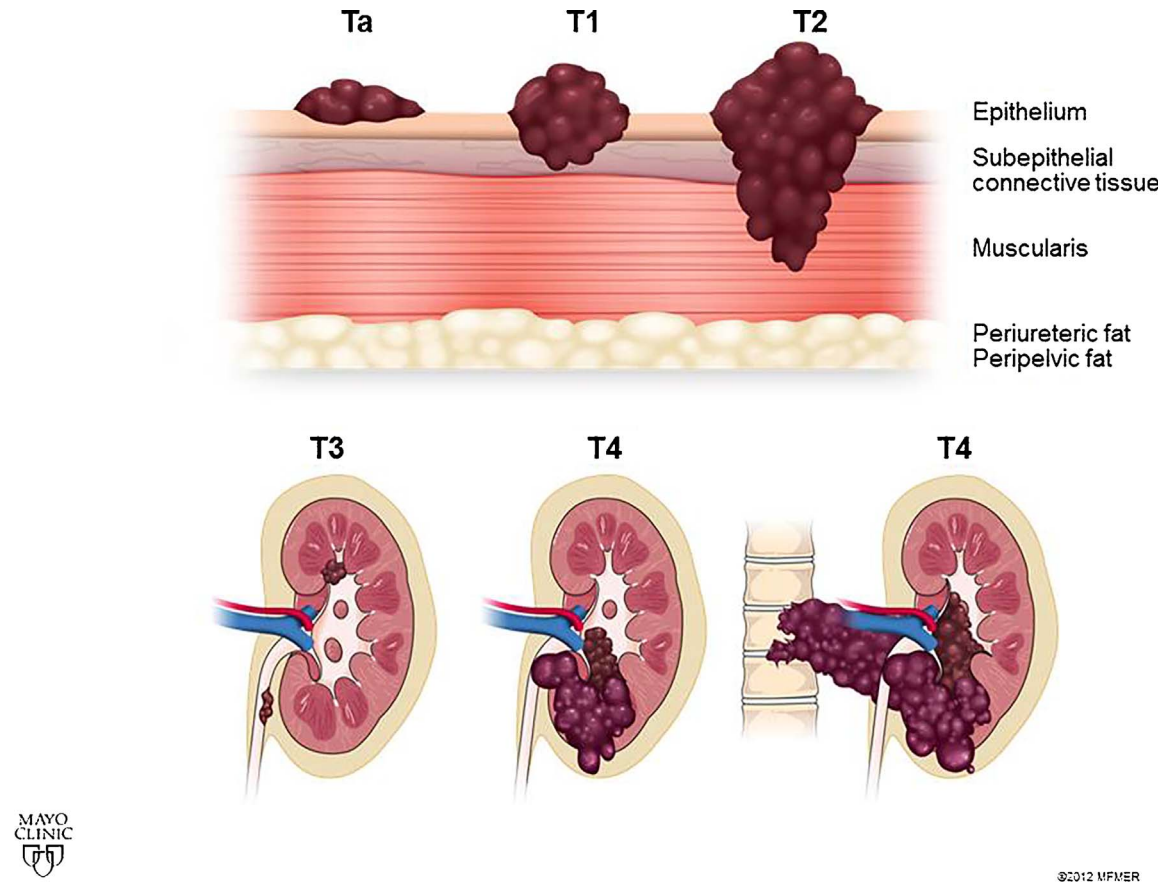

Fig. 1. Upper tract T staging. Ta (in situ) cancer is typically not apparent on imaging, and is detected endoscopically. T1 is superficial tumor, T2 muscle invasive. Locally advanced extension through the ureteral wall to the periureteral/pericalyceal fat is stage T3. Invasion of the renal parenchyma or any retroperitoneal structures beyond fat is stage T4. Modified from Reference 2.

Table 1
TNM staging of upper tract urothelial carcinoma. Sobin L, Gospodarowicz M, Wittekind C. TNM classification of malignant tumours. Urological tumours, renal pelvis and ureter. ed. 7. rev. New York, NY: Wiley-Blackwell; 2009. p. 258–61.

T stage (primary mass)	
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ*
T1	Invasion of subepithelial connective tissue
T2	Muscle invasion
T3	Renal pelvis mass: invasion of peripelvic fat or renal parenchyma Ureter mass: invasion of periureteral fat
T4	Invasion of adjacent organs/structures, or through the kidney to perirenal fat
N stage (lymph nodes)	
N0	No lymph node involvement
N1	Single positive lymph node, not more than 2 cm in size
N2	Single positive lymph node (2–5 cm in size), or multiple lymph nodes all < 5 cm in size
N3	Metastatic node > 5 cm in size
M stage (distant metastasis)	
M0	No distant metastasis
M1	Distant metastasis present

imaging has been shown to be an independent predictor of invasive and high grade disease and should be specifically noted. [13]

1.3. Similarities and differences of UTUC from UCB

Pathologic grading, staging, and morphology are similar between UTUC and UCB but the diseases do show some notable differences. While carcinoma in situ has a better prognosis in the upper tract than in the bladder, there are overall worse outcomes with UTUC compared to UCB [14]. Some theorize that this difference in prognosis may be related to limitations of our staging systems and treatment limitations rather than tumor biology, as there are much higher rates of disease upstaging/upgrading for UTUC at surgery and intracavitary therapy is much less effective with UTUC. Gender is another point of distinction between UTUC and UBC as it does not seem to have the independent prognostic significance for UTUC as it does for UBC. Additionally, the role of lymphadenectomy is unclear for UTUC, whereas it is well established with radical cystectomy. [15]

1.4. Treatment

Typically, radical nephroureterectomy (RNU) with bladder cuff excision is considered the gold standard therapy for non-metastatic UTUC [9] although kidney sparing surgery, typically performed endoscopically, may be offered in carefully selected cases for low-risk tumors (unifocal, < 1 cm, low grade, with no imaging findings of locally invasive behavior) or in a solitary kidney. High grade and large, invasive tumors may warrant lymphadenectomy and consideration of