

Diagnosis, workup, and risk stratification of upper tract urothelial carcinoma

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Abstract: Upper tract urothelial carcinoma (UTUC) is a relatively rare disease that presents unique challenges to urologists from both a diagnostic and management standpoint. UTUC is a clinically heterogenous disease with a varied natural history, and given its location in the upper urinary tract, treatment has the potential to cause or worsen chronic kidney disease. Therefore, physicians caring for patients with UTUC must be facile with multiple diagnostic and therapeutic strategies in order to provide optimal patient care. We present an overview of the epidemiology, histology, risk factors, and contemporary approach to the diagnosis, laboratory evaluation, imaging, and risk stratification for patients with UTUC. Computerized tomographic urography, thorough endoscopic evaluation, and biopsy (endoscopically or percutaneously) remain the standard of care for the diagnosis and staging of patients with suspected UTUC. Preoperative nomograms are vital to select patients more optimally for preoperative systemic chemotherapy and facilitate clinical trial enrollment. A thorough understanding of the various diagnostic challenges, imaging/pathologic limitations, biomarkers, and risk stratification tools will allow us as a field to develop new modalities to improve our diagnostic capabilities and reduce the risk of under diagnosis and over treatment for our patients.

Keywords: Upper tract urothelial carcinoma (UTUC); ureteroscopy; biopsy; risk stratification

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Introduction

Urothelial carcinoma of the ureter, renal pelvis, and intrarenal collecting system comprises about 5–10% of all urothelial carcinomas and is collectively termed upper tract urothelial carcinoma (UTUC) (1-3). UTUC is a clinically heterogenous disease with a varied natural history, and given its location in the upper urinary tract, treatment has the potential to cause or worsen chronic kidney disease. Accordingly, physicians caring for UTUC patients must be facile with multiple diagnostic and therapeutic strategies in order to provide optimal patient care. The objective of this review is to outline contemporary approaches to diagnosis, workup, and risk stratification for patients with UTUC.

Epidemiology and risk factors

Epidemiology

The incidence of UTUC has been estimated at 2 cases per

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100,000 persons in the Western Hemisphere (2,4,5). The incidence is slowly rising over the past 3 decades, and there is also recent evidence of a migration towards higher stage disease at diagnosis, with the largest increase observed for *in situ* disease (2,6,7). Tumors of the renal pelvis are twice as common as ureteral tumors, and although the majority of tumors occur in a single renal unit, about 5% of UTUCs are bilateral at diagnosis (8,9). Concurrent bladder tumors are common and are found in 17% of cases (10).

The median age at diagnosis of UTUC is 73 years (4). There is a well-described sex disparity in the occurrence of UTUC, with a 2:1 male to female incidence ratio (4,11). While the majority of patients diagnosed with UTUC in the United States are Caucasian, incidence is increasing among racial minorities. In a study utilizing the Surveillance, Epidemiology, and End Results database examining trends in UTUC from 1973 to 2005, incidence was noted to increase among Black patients (3.4% to 4.3%) as well as those of 'Other' race (4% to 7.5%), including those of Asian, American Indian/Alaskan Native, or Hawaiian/ Pacific Islander descent (4). Following treatment, the most frequent site of UTUC recurrence is in the bladder, which occurs in about 1/3 of patients (12,13). In those patients with low-risk disease manage endoscopically, ipsilateral recurrence rate approaches 35% (14). Recurrence in the contralateral upper tract is much less common, occurring in 5% of cases (15).

Risk factors

Tobacco exposure is the primary risk factor for developing UTUC, with an estimated 25-60% of cases attributable to smoking (16). There is also a dose-response relationship between tobacco exposure and UTUC. The relative risk for developing UTUC among smokers in the United States is around 3, but this increases to a relative risk of 7.2 among those with greater than 45 pack-years of tobacco exposure (16,17). Importantly, this risk is also modifiable, as smoking cessation is associated with a 60% to 70% reduction in risk 10 or more years after quitting (16). Urothelial carcinogenesis is thought to be potentiated by N-hydroxylamine, which is a metabolite of several aromatic amines contained in tobacco smoke. Susceptibility to the carcinogenic effects of smoking is likely influenced by genetic polymorphisms in enzymes that degrade N-hydroxylamine, which may also lead to increased susceptibility within families (18).

Several additional environmental exposures are also

implicated in risk of UTUC. Occupational exposure to aromatic amines in petroleum, industrial dyes, textiles, plastic manufacturing and coal are linked to developing UTUC (19). Exposure to aristocholic acid is similarly associated with an increasing risk of UTUC. This is thought to underlie the dramatically increased incidence of UTUC that occurred in rural areas of the Balkans (Serbia, Bulgaria, Romania, Croatia and Bosnia and Herzegovina) in the mid-20th century. Termed Balkan Endemic Nephropathy, residents here had a risk 60-100 times higher than those living in other parts of the world (19). Flour made from wheat contaminated with aristocholic acid from Aristocholia clematitis, a native Balkan plant, likely played a role (20). However, cases in the Balkans are decreasing over more recent years (21). Aristocholic acid is also found in some Chinese herbal products and teas, and indeed a higher incidence of UTUC is observed in Chinese mainland and Taiwan (19). Chronic exposure to arsenic in drinking water, usually due to contaminated wells, is also associated with developing UTUC (22). Use of the analgesic phenacetin has been associated with nephrotoxicity and risk of UTUC (23). Although routine use of phenacetin has been abandoned, analgesic abuse more broadly, including codeine, acetaminophen, and salicylates, has retained an association with increased risk of upper tract tumors (24). Chronic urinary tract inflammation and history of exposure to alkylating chemotherapies, such as cyclophosphamide, are further linked to risk of UTUC (19,25).

A history of urothelial carcinoma of the bladder is another well-known risk factor for UTUC, with rates of upper tract recurrence ranging from 1-6% following radical cystectomy in modern series (26,27). Although there is a theoretical risk of seeding the upper urinary tract if a ureteral stent is placed at the time of endoscopic resection of a bladder tumor, the available data are mixed regarding whether this is a clinically meaningful phenomenon. Miest and colleagues undertook a multi-institutional review of 1,049 patients who underwent radical cystectomy at one of two centers and observed no difference in the rate of subsequent upper tract recurrence between patients managed with a ureteral stent or nephrostomy tube preoperatively (28). However, Sountoulides et al. undertook a systematic review of the risk of metachronous UTUC recurrence after a bladder tumor, and found that among patients without preoperative hydronephrosis, subsequent UTUC was more common in those who had a ureteral stent placed after resection versus those who did not [odds ratio (OR) 3.37, 95% confidence interval (CI): 1.49-7.63] (29).

1458

Notably, this was not found among those with preoperative hydronephrosis, as no significant difference in upper tract recurrence was seen between those managed with a ureteral stent or a nephrostomy tube in this population. Authors concluded that prophylactic ureteral stenting after ureteral orifice resection should be avoided, when possible, in patients without preoperative hydronephrosis due to the potential for upper tract seeding (29).

Lynch syndrome related cancers

A hereditary predisposition to UTUC is known to occur in the context of Lynch syndrome, also termed hereditary nonpolyposis colorectal carcinoma (HNPCC) (30). UTUC is the 3rd most common tumor in HNPCC, occurring in about 5% of patients; colon (63%) and endometrial (9%) cancers also frequently occur (30). Lynch syndrome has an autosomal dominant mode of transmission and is caused by a mutation in one of several DNA mismatch repair genes, including MLH1, MSH2, MSH6 and PMS2 (30). The potential for a hereditary UTUC should be suspected in patients who present at a young age (<60 years), who have a personal history of another cancer in the HNPCC spectrum (including colon, endometrial, pancreatic, ovarian and gastric cancers), or among those with two or more firstdegree relatives with a Lynch spectrum cancer (30,31). Tissue-based testing for HNPCC includes polymerase chain reaction testing for high microsatellite instability within the tumor, a hallmark of Lynch syndrome, as well as with immunohistochemistry evaluating for loss of MLH1, MSH2, MSH6 and PMS2 (31). Suspected or identified individuals should be referred for genetic counseling. For individuals known to have Lynch syndrome, screening for UTUC with an annual urinalysis is recommended, along with consideration for periodic upper tract imaging (31).

Histology

Urothelial carcinomas are the most common tumors of the upper urinary tract, representing over 90% of cases (32). Approximately 24% of cases include histologic variants, including squamous, glandular, sarcomatoid, micropapillary or neuroendocrine differentiation (33). Primary squamous cell carcinomas or adenocarcinomas can occur in the upper urinary tract but are very rare, representing <1% of upper tract tumors (23,34).

Benign lesions of the upper tract are also known to occur, including papillomas, inverted papillomas, and von Brunn nests. Concurrent or subsequent malignancy has been observed in 15–20% of patients with inverted papillomas of the upper tract, and therefore upper tract surveillance is recommended for these patients for at least 2 years (35-37). Other benign lesions that can occur in the upper tract include fibroepithelial polyps and neurofibromas, which are best treated with local excision (38,39).

Diagnosis and workup

Presenting symptoms

The most common symptom of UTUC is gross or microscopic hematuria, which is present in 75–80% of cases (32). Gross hematuria is predictive of higher pathologic stage at initial presentation compared to microscopic hematuria (40). Flank pain due to renal obstruction occurs in 20% of patients (32). Occasionally, UTUC is diagnosed incidentally in otherwise asymptomatic patients with evidence of a collecting system mass on cross-sectional imaging. Hydronephrosis is often present on imaging (up to 50% of cases), and multiple studies have shown that hydronephrosis is associated with higher stage at diagnosis (41,42). Constitutional symptoms, including weight loss, fever, night sweats, anorexia, or hemoptysis are associated with a worse prognosis and should prompt a complete evaluation for the presence metastatic disease (32).

Laboratory evaluation

Basic laboratory workup should include microscopic urinalysis to detect microscopic hematuria and rule out urinary tract infection, along with hemoglobin level and renal function panel. Cytology remains a reliable diagnostic method for UTUC, however voided urinary cytology has high false negative rates approaching 50-90% (43). Selective cytology of the affected upper tract has shown improved diagnostic accuracy compared to voided cytology, with meta-analysis demonstrating a sensitivity of 53.1% and specificity of 90% (43). Newer classification methods in cytologic grading (Paris System) were introduced in 2016 to improve diagnostic accuracy and focus more on high-grade diagnosis (44). Subsequent studies have demonstrated a significantly higher rate of surgical pathologic concordance when compared with traditional cytology in UTUC (45). Additionally, high rates of sensitivity (71-78.6%) and specificity (86-100%) have been found (46,47); while others report a decrease in sensitivity when compared to traditional

cytology (48). Despite these diagnostic challenges, both the European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) recommend the addition of cytology to the initial evaluation of a patient with suspected UTUC (49,50).

Given the current limitations with non-invasive means for diagnosis of UTUC, the role of alternative urinary biomarkers has been an active area of investigation. Fluorescence in situ hybridization (FISH) testing involves the use of fluorescent probes to identify abnormalities in specific chromosomes (3, 7, 17, and 9p21) (51). While FISH is commonly used adjunctly to aid in the diagnosis of bladder cancer, efforts have been made to apply it to the diagnosis of UTUC with mixed results. When used to analyze voided urine without a concurrent bladder tumor, sensitivity and specificity have varied widely, with reported rates of 54-76.7% and 78-94.7%, respectively (52,53). The detection of DNA mutations and methylation markers in urine has gained some attention as another potential biomarker for UTUC, with preliminary studies showing promise. Monteiro-Reis et al. studied 22 patients with confirmed UTUC and found that by analyzing voided samples for methylation of the GDF15, TMEFF2, and VIM promoters they were able to detect UTUC with 91% sensitivity and 100% specificity (54). Similarly, Guo et al. examined the same panel with the addition of the CDH1, HSPA2, and RASSF1A genes, and found a lower sensitivity of 82% and specificity of 68% (55). Neither study evaluated whether methylation could distinguish between upper and lower tract lesions. Several gene mutations have been linked to urothelial carcinoma, and mutations in hotspots of the TERT and FGFR3 genes have been studied as potential urinary biomarkers for UTUC. One study found that when examining TERT and FGFR3 mutations in combination with cytology, a sensitivity of 78.6% and specificity of 96% was demonstrated (56). Despite sometimes promising results, urinary biomarkers for UTUC have failed to achieve mainstream support or guideline endorsement.

Imaging

Computerized tomographic urography (CTU) is the dominant imaging modality for evaluating the upper urinary tract. It has been shown to be highly accurate for diagnosing UTUC, with sensitivity of 92% and specificity of 95% according to a recent meta-analysis of 13 studies involving 1,233 patients (57). Additionally, it is widely available, able to detect lesions as small as 5 mm (58), and can offer additional staging information-with the presence of enlarged lymph nodes being highly predictive for metastasis in UTUC (59). Current radiological methods cannot diagnose invasiveness unless the tumor is advanced. Magnetic resonance urography (MRU) may be used in patients who cannot undergo CTU, typically when iodinated contrast media is contraindicated because of severe allergy or poor renal function. However, MRU has a lower sensitivity (69-75%) for the diagnosis of UTUC compared to CTU, and its utility can be limited by motion/ peristalsis artifact, increased study time, and cost (60-62). Retrograde pyelogram at the time of cystourethroscopy is also an option for patients with contraindications to CTU/MRU, however the sensitivity for UTUC is lower (25-100%) and provides no staging information (63). CT remains the preferred diagnostic modality for complete staging and detecting metastasis, however the use of ¹⁸F-fluorodeoxglucose positron emission tomography/ computed tomography (FDG-PET/CT) has shown to be effective in detecting nodal metastasis with a sensitivity and specificity of 82% and 84%, respectively (64). Currently, only the EAU have specific imaging guidelines for the diagnosis of UTUC-with CTU being the preferred modality for diagnosis and staging (49).

Endoscopic evaluation

Cystourethroscopy remains an integral initial part of UTUC evaluation to rule out concomitant bladder cancer. A retrospective review of 673 patients diagnosed and treated for UTUC found that 17% of patients presented with both UTUC and bladder cancer—with the location of the UTUC (renal pelvis *vs.* upper ureter *vs.* lower ureter) being the only predictive factor for concomitant bladder tumor on multivariate analysis (OR: 1.7; 95% CI: 1.007–2.906, P=0.047) (10). This can be done at the time of ureteroscopy or in the office pending the clinical scenario and imaging findings.

The use of ureteroscopy with biopsy is currently the primary method for diagnosing UTUC if the imaging and cytology are not sufficient for the diagnosis and/or riskstratification of the tumor (49,50). Flexible ureteroscopy allows visualization of the ureter, renal pelvis and collecting system and enables selective urinary cytology as well as biopsies for suspicious lesions or positive urinary cytology with negative enhanced cystoscopy. The specific size, appearance, and multifocality of UTUC can also be fully characterized—especially with the emergence of thinner

flexible ureteroscopes with digital technology and image enhancement techniques (65,66). Talso et al. compared seven different flexible ureteroscope systems (Olympus V, Olympus V2, Olympus P6, Wolf Cobra vision, Storz Flex XC, Storz Flex X2, and Lithovue) and found that the newer digital scopes offered better image quality than fiber optics (65). Narrow-band imaging (NBI), which has shown higher detection of bladder tumors with greater sensitivity on meta-analysis compared to white-light cystoscopy (67), has been evaluated in UTUC in two small prospective studies with promising but preliminary results (66,68). Confocal laser endomicroscopy (CLE) enables real-time in vivo visualization of tissue microarchitecture and cellular morphology using a low-energy laser light source and has been shown in small case series to have high concordance with definitive histology (69,70).

While there have been improvements in the visualization of UTUC, the endoscopic yield of biopsies remains a key factor in the reliability of risk stratification for UTUC. Acquisition of adequate samples of a sufficient quality and size for accurate pathologic interpretation is a technical challenge-mainly limited by the size of current ureteroscopes while maintaining their necessary maneuverability. There are numerous ureteroscopic biopsy devices that have been evaluated for their efficacy and utility-the 3F cold-cup biopsy forceps (Piranha), 6F BIGopsy[®] backloading cold-cup biopsy forceps, and 2.2/2.4F stone wire basket are the most common (71-73). Retrospective cohort studies have found diagnostic rates of 74.9–79% for 3F cold-cup forceps, 81.9–90% for BIGopsy[®], and 87-100% for 2.2F or 2.4F wire baskets (71-73)-with small size of sampled tissue being the main driver of false negatives (74,75). Forceps (either 3F forceps or BIGopsy[®]) are generally preferable for sampling smaller, flat, or nonpapillary lesions, while the basket can be used to debulk large papillary tumors by avulsing large pieces of tumor. A newer ureteroscopic biopsy technique called the "form tackle" was recently described by Klett et al. (76) and was compared to standard biopsy techniques in a case series of 12 patients. In each patient they performed a "standard biopsy" with a 3F cold-cup biopsy forceps and a second biopsy utilizing the same biopsy forceps and the new "form tackle" technique. This new biopsy technique involves engaging the jaws of the forceps into the base of the tumor and advancing both the ureteroscope and biopsy forceps "forward, up, and away" from the mucosal wall until the tissue is released. Using the new technique, UTUC was diagnosed in an additional 4 patients (2 low-grade, 2 high-grade) in the setting of a

benign "standard technique" biopsy.

While using larger biopsy devices, different techniques, or taking multiple biopsies can enhance the quality/size of the biopsy, it has been suggested that addition of cytology should be mandatory to improve grading accuracy (75). Several studies have demonstrated the grade concordance of ureteroscopic biopsy with radical nephroureterectomy pathologic specimens is estimated between 68-77% (72,73). This discordance is also influenced by the overall size of tumor, as multiple small biopsies may only provide pathologic data for a small region and potentially miss high-grade morphology. Breda et al. found that only in tumors less than 2 cm is there a high concordance between ureteroscopic biopsy grade and final pathology (72). Likewise, staging information is limited by the depth of urothelial tissue able to be sampled endoscopically (77). Vashistha et al. retrospectively reviewed 120 endoscopic biopsies for UTUC and found poor stage concordance (58.6%) between ureteroscopic biopsy specimen and final pathology at time of nephroureterectomy (74). Similarly, Lama and colleagues found agreement between the biopsy grade and final pathologic stage occurred in 58% of patients in their multi-institutional retrospective collaboration with 145 patients (73). A recent comprehensive systemic review and meta-analysis was performed utilizing 23 studies (almost 3,600 patients) to evaluate the accuracy of ureteroscopic biopsies in predicting the stage and grade of UTUC (78). Interestingly, they found a substantial correlation between tumor grade at ureteroscopic biopsy and the final pathology (66%, 95% CI: 55-77%) for low-grade tumors and 97% (95% CI: 94-98%) for high-grade tumors. Additionally, the stage-to-stage match between ureteroscopic biopsy/ final pathology showed a positive predictive value (PPV) for cT1+/muscle-invasive disease of 94% (95% CI: 84-100%) and a NPV for cTa-Tis/non-muscle-invasive disease of 60% (95% CI: 52-68%). These data demonstrate that invasion of the subepithelial connective tissue in the ureteroscopy specimen has a strong correlation with pathologic stage, however biopsy of the subepithelium is one of the main challenges of ureteroscopic biopsy (77). Nevertheless, a certain risk of undergrading and understaging should be assumed.

Additionally, various clinical scenarios can present significant challenges for the use of diagnostic ureteroscopy (previous urinary diversion, difficult calyceal anatomy, severe hematuria, etc.) leading some authors to investigate the safety, diagnostic yield, and histologic concordance of a percutaneous biopsy approach for diagnosing UTUC.

Huang et al. found that 85% of patients undergoing percutaneous biopsy for various indications (nondiagnostic ureteroscopy, urinary diversion, or being poor surgical candidates) received a diagnosis of UTUC-with 86% grade concordance with final pathology (79). However, similar to ureteroscopic biopsy, percutaneous biopsy has limited ability to stage the disease. The largest series of percutaneous biopsy for UTUC was published by Joseph and colleagues in 2020 and included 42 patients from 2009–2017 undergoing radical nephroureterectomy. They demonstrated 95% histologic concordance and 90% grade concordance relative to final nephroureterectomy pathology. Additionally, at a median follow-up of 28.2 months no cases of radiographic tract seeding were identified (80). The lack of tract seeding in this series [and Huang et al. (79)] was felt to be due to improved biopsy technique and incorporation of coaxial needle sets-which utilize a larger outer introducing needle for the initial insertion with multiple biopsies taken through the introducer needle to minimize the risk of tract seeding.

In addition to low risk of tract seeding with percutaneous biopsy, this approach may also decrease the risk of intravesical recurrence. A recent meta-analysis by Sharma et al., comparing ureteroscopy vs. no ureteroscopy prior to nephroureterectomy found that 8 out of 12 studies demonstrated an increased risk for intravesical recurrence if ureteroscopy was performed. On multivariate analysis, ureteroscopy with biopsy was found to increase the risk of intravesical recurrence [hazard ratio (HR) 1.40, P=0.04], while ureteroscopy alone and percutaneous biopsy did not (HR 1.07, P=0.87; HR 1.15, P=0.54 respectively) (81). Similarly, Douglawi and colleagues retrospectively reviewed 143 patients who underwent radical nephroureterectomy for UTUC and found higher bladder recurrence rates for patients who had ureteroscopy prior vs. no ureteroscopy [30.8% vs. 7.7%, respectively (P=0.02)] (82). Interestingly, a lower recurrence rate was noted in patients whom a ureteral access sheath was utilized (11.5%) vs. those with no access sheath (39.7%, P=0.01)-potentially suggesting a protective effect of the ureteral access sheath. Multivariable analysis confirmed a significant increase in bladder recurrence if ureteroscopy was performed prior to radical nephroureterectomy [HR 5.6 (1.7-18.5), P<0.004), however, this effect was mitigated if a ureteral access sheath was used [HR 1.3 (0.3-6.4), P=0.76]. These data-along with other studies demonstrating the clonal relatedness of UTUC/ subsequent bladder tumors (83), a decreased risk of bladder recurrence after nephroureterectomy with a single instillation

of postoperative intravesical chemotherapy (12,13), and extrapolation from the post-TURBT setting (84) support the rationale for use of prophylactic intravesical chemotherapy after endoscopic biopsy to prevent bladder seeding, however this approach needs to be validated with future studies.

Risk stratification

Patient and tumor-related factors

UTUC is more common in men than women, and previous research has suggested that female gender may be associated with a worse oncologic outcome. However, after taking other prognostic factors into account (such as age, pT stage, neo/adjuvant chemotherapy, etc), no significant difference in cancer-specific survival or overall survival was found between genders on systematic review and meta-analysis (85). The relationship between ethnicity and UTUC outcomes is also uncertain, with some studies finding differences in survival between ethnic groups and others finding no significant differences (86). Whether these potential differences are related to biology or access to care is unknown. Older age at the time of radical nephroureterectomy has been shown to be independently associated with decreased cancer specific survival (87). Similarly, smoking is a wellestablished risk factor for UTUC, with long-term smokers at higher risk of more advanced disease stage, recurrence after radical nephroureterectomy, and cancer-specific mortality (88). Various medical comorbidities (chronic kidney disease, obesity), preoperative laboratory abnormalities (hypoalbuminemia, elevated C-reactive protein, elevated fibrinogen) along with poor performance status are also associated with worse survival outcomes across disease stages (89-91). Constitutional symptoms, including weight loss, fever, night sweats, anorexia, or hemoptysis are associated with a worse prognosis and should prompt a complete evaluation for the presence metastatic disease (32).

While there are certainly some patient related factors that are prognostic, the most accurate independent factors for predicted outcome in UTUC remain tumor grade and stage (87,92-94). In a study of UTUC patients in the Netherlands, 5-year cancer-specific survival was 86% for non-muscle-invasive tumors, 70% for muscleinvasive, organ-confined tumors, and 44% for locallyadvanced tumors (95). Another contemporary analysis of radical nephroureterectomies for UTUC showed that 5-year cancer-specific survival was 86% for T1N0, 77%

for T2N0, 63% for T3N0, and 39% for T4N0/T any N1-3 (96). Hydronephrosis is often present on imaging (up to 50% of cases), and multiple studies have shown that hydronephrosis is associated with higher stage at diagnosis (41,42). Additionally, after adjusting for tumor stage, patients with ureteral and/or multifocal tumors appear to have a worse prognosis than patients with renal pelvic tumors (97,98). Larger tumors are more likely to be muscleinvasive and/or non-organ-confined in both ureteral and renal pelvis UTUC-with 2 cm being the best cut-off in identifying patient's with an increased risk of pT2 UTUC or higher (99). Variant histology in UTUC has also been found to be associated with worse recurrence free survival, cancer specific survival, and overall survival on a recent systematic review and meta-analysis of 26 studies with over 1,200 patients-with micropapillary and squamous and/ or glandular variant histologies being associated with the worst cancer specific survival (100). Additionally, while previous studies have found mixed results with respect to previous/concomitant bladder cancer and CSS in patients with UTUC, a recent Surveillance, Epidemiology, and End Results (SEER) database review of 8,500 patients found that UTUC patients with previous or concomitant bladder cancer had a worse prognosis and higher risk of intravesical recurrence after radical nephroureterectomy (101). Various pre-operative serum and urine-based biomarkers have been investigated to help predict the prognosis of UTUC, however none of the investigated markers have been validated yet to support their introduction into routine clinical decision-making.

Prognostic tools

Several models have been developed to predict highgrade, muscle-invasive, or non-organ confined disease in UTUC based on various prognostic factors. Brien and colleagues utilized a combination of hydronephrosis, positive urinary cytology, and high-grade disease on biopsy to predict muscle invasive carcinoma at the time of radical nephroureterectomy. All three variables were independently associated with non-organ confined diseased and abnormality of all three had 89% and 73% positive predictive value for muscle invasive and nonorgan confined UTUC, respectively, but when all tests were normal, the negative predictive value was 100% (42). In the same year, Margulis *et al.* proposed a different model to predict nonorgan confined disease with an accuracy of 77% based on tumor grade, architecture, and location (102). In a subsequent follow-up multi-institutional retrospective study, a new multivariable model was developed and demonstrated that clinical stage (OR 14.0, P<0.01), biopsy tumor grade (OR 3.3, P=0.01), tumor architecture (OR 2.65, P=0.09), and hemoglobin (OR 0.8, P=0.02) level were independently associated with non-organ confined disease. A preoperative nomogram incorporating these 4 variables achieved 82% accuracy, 48% sensitivity, and 95% specificity in predicting non-organ confined UTUC (103). These preoperative nomograms can be used to select patients more optimally for preoperative systemic chemotherapy and facilitate clinical trial enrollment—although some caution should be used as none have benefited from external validation.

Because clinical stage is so difficult to determine preoperatively, the EAU guidelines for UTUC have proposed stratifying patients as either low or high risk for progression in order to identify patients who are more likely to benefit from kidney-sparing treatment and those who should be treated with radical surgery (49). Based on the previously mentioned risk data and prognostic tools, the EAU proposed a set of parameters for pretreatment risk stratification of UTUC to support clinical decision-making. A low-risk tumor is defined as unifocal disease, lesion <2 cm, low-grade cytology/biopsy, and no invasive aspect on imaging (all must be present). High-risk tumors include those presenting with hydronephrosis or multifocal disease, any high-grade status (on cytology or biopsy), or lesions >2 cm. A history of radical cystectomy or variant histology are also criteria for high-risk tumors. Any of these high-risk features make it a high risk UTUC (Table 1). The predictive ability of the EAU risk stratification system to identify $\geq pT2/N+$ stage patients at radical nephroureterectomy was recently evaluated and compared to a new preoperative risk model utilizing over 1,200 patients in a multi-institutional retrospective cohort. This new model utilized age, high-grade biopsy, cT1+ biopsy, preoperative hydronephrosis, tumor size, invasion on imaging, and sessile tumor architecture to achieve an accuracy of 75%-compared to 71% for the EAU risk stratification system (104). Additionally, several new risk stratification strategies have been evaluated in comparison to the EAU risk grouping-including a tumour grade-and stage-based model (105) and a three-tier risk stratification model (i.e., low-, intermediate-, and high-risk) (106). Both strategies demonstrated a potential improvement on the current EAU risk stratification system but require further external validation.

Table 1 EAU risk stratification of non-metastatic UTUC

Low-risk UTUC (all criteria must be present)	
Unifocal disease	
Tumor size <2 cm	
Low-grade cytology	
Low-grade biopsy	
No invasive aspect on imaging	
High-risk UTUC (any criteria may be present)	
Hydronephrosis	
Tumor size >2 cm	
High-grade cytology	
High-grade biopsy	
Multifocal disease	
Previous radical cystectomy for bladder cancer	
Variant histology	
FALL European Association of Urology: UTLIC ur	ne

EAU, European Association of Urology; UTUC, upper tract urothelial carcinoma.

Conclusions

UTUC is a relatively rare disease that presents unique challenges to urologists from both a diagnostic and management standpoint. It is imperative to understand the epidemiology, natural history, genetics and known risk factors for this malignancy. Additionally, a thorough understanding of the diagnostic challenges, imaging/ pathologic limitations, patient comorbidities, and risk stratification tools will allow us as a field to develop new modalities to improve our diagnostic capabilities and reduce the risk of under diagnosis and over treatment for our patients.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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1464

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1466

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1468

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