

Contemporary management of upper tract urothelial cell carcinoma

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Abstract

Upper tract urothelial cell carcinoma (UTUCC), formerly known as transitional cell carcinoma of the upper urinary tract, is a rare oncologic disease in Western countries.

Thus its disease process and its management are not as well defined as other urologic cancers. We are reviewing the current evidence based literature available to develop a plan for the treatment of UTUCC. A PubMed search was completed using the key words "upper tract urothelial cell carcinoma", "epidemiology", "risk factor", "treatment" and "prognosis". Six hundred fifty two articles were found. We narrowed our search to articles published between January 2004 and June 2016 for a more contemporary review of the topic. Four hundred seventy articles were then available for review. Further detailed search was performed for relevance on the topic and hundred one articles were selected for the review. Many risk factors have been found to be associated with the development of UTUCC, including tobacco use. Patients are often asymptomatic and may only present with microscopic or gross hematuria. Tumor grade and stage are pivotal in determining the treatment options for UTUCC. Advancements in endoscopic techniques have aided in the diagnosis, grading and treatment of this disease. Treatment options include topical therapy, with combinations of methotrexate, vinblastine, doxorubicin and cisplatin or gemcitabine or cisplatin, endoscopic resection, segmental ureterectomy and ureteral implantation, and nephroureterectomy, including bladder cuff. Treatment recommendations depend on tumor grade and stage, renal function, tumor location and the patient's prognosis. There are currently no tissue or blood-based biomarkers available to accurately monitor the disease. Further studies of gene expression and biomarkers may hopefully improve the management of this disease. Although rare in many countries, UTUCC is becoming more prevalent due to exposure to carcinogenic herbal remedies and other identifiable risk factors. Numerous treatment modalities, both surgical and chemotherapeutic, have been utilized to treat both low and high grade UTUCC tumors. Additional clinical trials are necessary to further develop methods for screening, treatment, and surveillance to improve management.

Key words: Urothelial cell carcinoma; Diagnosis; Upper tract; Epidemiology; Risk factors; Treatment; Prognosis

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Core tip: To review the current literature on upper tract urothelial cell carcinoma (UTUCC) and provide a contemporary management plan for treatment based on best available evidence. Large randomized controlled trials are lacking in UTUCC due to the fortunately rare occurrence of the disease. Treatment recommendations for the primary lesion, imaging, and follow-up in this review are based on the stage and grade of the tumor. Early diagnosis and aggressive treatment remains the mainstay of therapy for UTUCC.

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INTRODUCTION

Upper tract urothelial cell carcinoma (UTUCC) accounts for 95% of upper tract carcinoma, with the remaining types being squamous cell carcinoma and adenocarcinoma^[1]. Although UTUCC is a rare disease in the West, with an incidence of approximately 40000 cases per year, the incidence has risen in recent years. It is more common and the incidence has risen quickly in Asian countries, especially Taiwan, along with the Balkan regions^[2].

UTUCC shares a similar embryologic origin as the bladder, both being derived from the urothelium. But due to anatomic, biological, and molecular differences between upper tract urothelial carcinoma and bladder cancer, they have been referred to as “disparate twin” diseases^[2,3]. Accurate local surgical staging and subsequent clinical staging (TNM) is important to help standardize treatment planning. Modern management of UTUCC includes chemotherapy, endoscopic procedures, and nephroureterectomy. We will review the epidemiology, risk factors, classification, diagnosis, staging and medical and surgical treatments of UTUCC.

EPIDEMIOLOGY

Upper tract urothelial cell cancer can be found with higher incidence in Balkan regions, and most recently in certain Asian countries especially in Taiwan^[2,4,5].

Upper tract urothelial cell cancers are most commonly diagnosed later in life, mostly in the eighth decade^[6]. However, it should also be considered in younger populations, especially in patients with exposure to aristolochic acid (AA) plants, which is commonly used for weight loss in Asian countries. It is a very uncommon disease, with an incidence of less than 1 case per 40000^[2]. It makes up 5% of all urothelial tumors and 5% to 7% of all renal tumors^[6]. Men are twice as likely to have UTUCC, compared to women^[7]. Although low in incidence, UTUCC

is very aggressive, as many patients are asymptomatic and tend to present later with advanced stage disease, often with metastasis. A thorough understanding of this disease is pivotal in successful diagnosis and treatment^[8].

RISK FACTORS

The most well known risk factor for UTUCC is aristolochic acid plants, more commonly used in Balkan regions and in Asian countries, especially in Taiwan^[4,9-12]. Balkan endemic nephropathy, associated with ingesting the aristolochic acid plants, can lead to renal failure and increased risk of UTUCC. In addition to increased exposure to aristolochic acid, Balkan populations are also known to have genetic and hereditary predisposition to UTUCC. Other risk factors are microsatellite instability and lynch syndrome type II^[13-16].

Other risk factors for UTUCC are similar to bladder urothelial cell carcinoma, with the most common risk factor being cigarette smoking^[7,17,18]. Tobacco use is found to increase the relative risk exposure from 2.5 to 7^[19]. Occupational exposures to chemicals such as petrochemical and plastic industries, ink solvents, coals, asphalt and aniline dye products are shared risk factors between UTUCC and bladder UCC^[20,21]. Newly identified risk factors associated with UTUCC include inverted papilloma which are found in the bladder^[22].

UTUCC can be associated with bladder urothelial cell carcinoma but occurs in less than 5%, although nearly 25% in patients with carcinoma *in situ* (CIS). Environmental exposures unique to upper tract tumors include Blackfoot disease, Artesian well water, weight-reducing pills, well water, arsenic, organic chlorides, and Ergot alkaloids^[5,23]. Phenacetin-based analgesics and cyclophosphamide have also been found to be causative agents in UTUCC.

PRESENTATION

UTUCC has been associated with significant delays in presentation, as many cases are asymptomatic. However, these cancers tend to be very aggressive once they present. Typically, it presents with microscopic or gross hematuria. Flank pain can be present in up to 30% of patients. This is often attributed to urinary tract obstruction by the tumor.

The most common locations for this tumor are the renal pelvis and less often the ureter. Ureteral tumors are located most commonly in the lower ureter and least commonly in the upper ureter. Incidence based on location is as follows: distal ureter in 70%, mid ureter in 25% and then proximal ureter in 5%^[24-26].

DIAGNOSIS

Contrasted imaging of the collecting systems and ureters with CT urogram or retropyelogram is necessary along with cystoscopy to diagnose UTUCC. UTUCC is most frequently identified as an obstruction or filling defect,



Figure 1 Filling defect on retropyelogram, showing typical “goblet sign” due to R ureteral urothelial cell carcinoma.

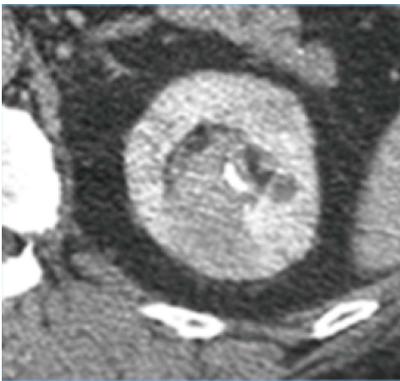


Figure 2 Central mass of upper tract urothelial cell carcinoma on left kidney, seen as renal sinus mass.

often known as the “goblet sign” when found in the ureter (Figure 1). CT urogram is the gold standard for both staging and diagnosis, with the sensitivity of 0.67-1 and specificity of 0.93^[19,27-31]. If the patient has renal failure or another reason to avoid intravenous contrast, a retrograde pyelogram can be performed. Suspect UTUCC if a central renal tumor is seen, as the mass grows into the renal sinus (Figure 2).

Physicians must have a high index of suspicion for UTUCC when faced with a positive cytology despite having a negative cystoscopy, especially high grade UCC and CIS^[32,33]. In this scenario, ureteral barbotage, also known as selective ureteral catheterization is performed^[34]. Ureteral washing has 80% sensitivity and ureteral brushing has 90% sensitivity. Of note, such selective collection of urine samples should occur prior to retrograde pyelography, as high-osmolar contrast agents may alter the cytologic features of the urine sample.

Once UTUCC is suspected, ureteropyeloscopy and biopsy is indicated^[35-37]. Coupled with biopsy, ureteropyeloscopy is the method of choice for diagnosis of UTUCC^[38-40]. However, due to the small size of the ureteral scopes, thin walled ureter and small biopsy forceps, staging is limited. Nevertheless, concordance between biopsy and final pathology is as high as 90% to 92%.

The TNM Staging System for UTUCC provided in Figure 3 and Table 1 defines the locations and extent of disease.

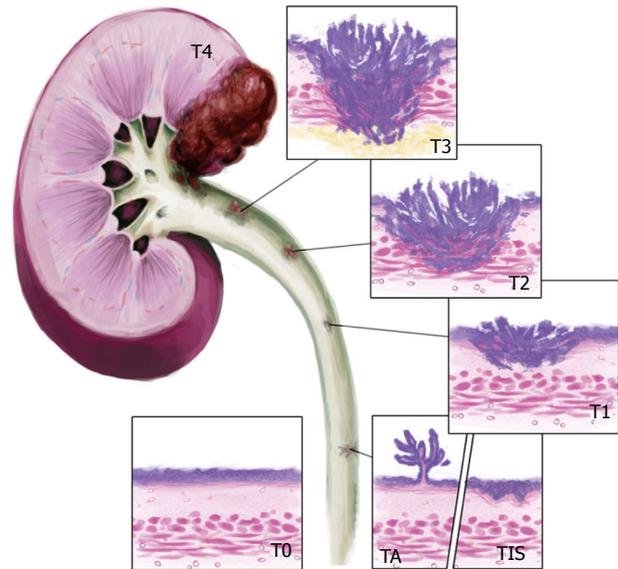


Figure 3 Pathologic stage of upper tract urothelial cell carcinoma. Courtesy of third year medical student at West Virginia University, Mike Tran.

The staging system begins at T0, which is no evidence of primary tumor and progresses to T4, where the tumor invades adjacent organs or through the kidney into the perinephric fat. Of note, tumor stage was identified as the most important determinant in predicting recurrence and survival. There for all efforts to obtain an accurately staged tissue is crucial^[41].

Lymph node involvement for renal pelvis tumors may include renal hilar, paracaval, aortic, and retroperitoneal nodes. For ureteral lymph node involvement, renal hilar, iliac, paracaval, periureteral, and pelvic nodes are commonly involved.

PROGNOSTIC FACTORS

The most pivotal factors in determining prognosis are tumor stage and grade^[42-46]. Invasion of the vascular, lymphatic, renal hilum and parenchyma, and perineural tissue surrounding the kidney has been shown to indicate more aggressive tumor behavior^[47-52]. Multifocal disease, including areas such as the bladder, have been found to indicate a higher likelihood of recurrence and a worse overall prognosis^[53]. Tumor necrosis greater than 10% is another independent risk factor indicating worse prognosis^[54,55]. Age, gender and tumor location have been found to offer little information on disease course and predicting overall prognosis^[56-61]. Numerous molecular markers including E-cadherin, Telomerase RNA component, hypoxia-inducible factor (HIF) 1- α , epithelial membrane protein 3, and C-erb-B2 have been investigated as possible diagnostic and prognostic tools^[62-66]. More data is needed before applying the markers in a clinical setting.

TREATMENT

Stage and grade of the tumor is instrumental in de-

Table 1 TNM classification

T - primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Papillary noninvasive carcinoma
Tis	Carcinoma <i>in situ</i>
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades the muscularis
T3	(For renal pelvis only) tumor invades beyond muscularis into peripelvic fat or the renal parenchyma T3 (For ureter only) tumor invades beyond muscularis into periureteric fat
T4	Tumor invades adjacent organs, or through the kidney into the 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, \leq 2 cm in greatest dimension
N2	Metastasis in a single lymph node, $>$ 2 cm but not $>$ 5 cm in greatest dimension; or multiple lymph nodes, none $>$ 5 cm in greatest dimension
N3	Metastasis in a lymph node, $>$ 5 cm in greatest dimension
M - distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

NCCN Guidelines® version 2, 2015^[19]. Upper GU tract tumors.

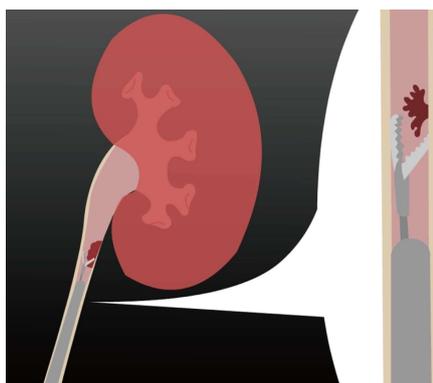


Figure 4 Obtaining tumor specimen for pathologic stage.

ciding treatment plans. Nephroureterectomy (NU) with bladder cuff has been the gold standard, and remains the treatment of choice for high grade (TA/T1, HG or CIS), invasive, or multifocal tumors, along with regional lymph node dissection^[42,67].

Segmental resection or distal ureterectomy may be indicated in select cases to preserve renal function^[68-70]. Tumors located in the distal third of the ureter can utilize a Psoas Hitch^[71,72] which was popularized by Turner-Warwick. This method is an effective means to bridge the resultant defect of the lower third of the ureter. However, a small contracted bladder is a contraindication due to insufficient bladder capacity.

Ureteral defects proximal to the pelvic brim require more than a Psoas hitch. A lengthy ureteral tumor or diseased ureter in a patient with a need to preserve renal function can utilize an ileal ureteral substitution. Relative contraindications for ileal ureteral substitution include renal insufficiency, bladder outlet obstruction, and inflammatory bowel disease.

Endoscopic resection or ablation can be considered in

patients with a solitary kidney or poor surgical candidates, especially for low grade and low stage tumors^[73-78]. Holmium or Nd: Yag may be used for tumor ablation, as well as ureteral resection *via* an ureteroscope (Figures 4 and 5)^[79].

A percutaneous approach may be considered in large ($>$ 1.5 cm) renal pelvis UCC that are grade 1 and possibly grade 2^[80,81]. The advantage for the percutaneous approach is that after 2-3 wk and with a normal nephrogram, BCG or mitomycin may be administered into the collecting system through the nephrostomy tube, as opposed to retrograde administration *via* reflux up a ureteral stent which is more challenging^[82-85]. The disadvantage for a percutaneous approach is that 1/3 will recur and it is more invasive than other treatment options.

There is a lack of prospective studies that use of chemotherapy, whether neoadjuvant or adjuvant, due to the low incidence of this disease. The National Comprehensive Cancer Network® (NCCN®) Clinical Practice Guidelines in Oncology (NCCN Guidelines®) suggest the use of both with patient discretion (Table 2). For muscle invasive UCC, MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) or gemcitabine and cisplatin chemotherapy are both treatment options^[85-91]. Of note, BCG and mitomycin treatment for upper tract UCC is extrapolated from bladder cancer and retrospective studies. There are currently no prospective studies showing improved survival and these are difficult to construct since it is such a rare disease. A role for BCG in the management of upper tract CIS has been demonstrated in retrospective studies, although a definitive efficacy of adjuvant topical therapy after endoscopic resection of Ta/T1 tumors has not yet been proven^[84,92]. Of note, immunotherapy and chemotherapy in the upper tract has limitations due to difficulty delivering them to the system, unlike bladder instillations with such agents. Currently NCCN Guidelines® support using postsurgical

Table 2 Adjuvant treatment for renal pelvis and urothelial carcinoma of ureter

Pathologic staging	Adjuvant treatment	Follow-up
pT0, pT1	None	Cystoscopy every 3 mo for 1 yr, then at increasing intervals Imaging of upper tract collecting system at 3- to 12-mo intervals, if endoscopic resection ± CT scan or MRI ± Chest X-ray
pT2, pT3 pT4, pN+	Consider adjuvant chemotherapy	Cystoscopy every 3 mo for 1 yr, then at increasing intervals Imaging of upper tract collecting system at 3- to 12-mo intervals ± CT scan or MRI ± Chest X-ray

NCCN Guidelines® version 2, 2015^[19]. Upper GU tract tumors. CT: Computed tomography; MRI: Magnetic resonance imaging.

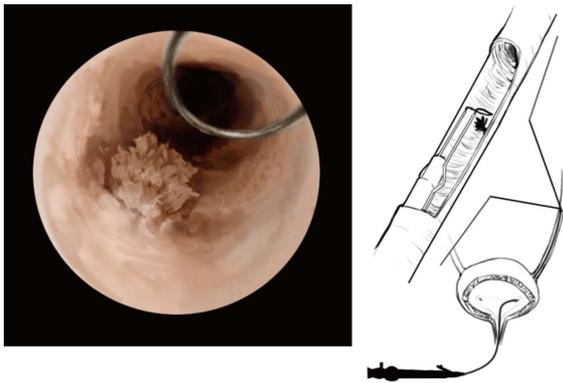


Figure 5 Tumor resection using ureteral resectoscope with loop.

intrapelvic chemotherapy or BCG for low grade UTUCC of the renal pelvis after endoscopic resection^[91].

Chemotherapy for metastatic disease was studied using MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) in 184 patients from 1986 to 2004 at M.D. Anderson Center. Median recurrence-free survival was 2.4 years^[75]. Patients with advanced disease should receive chemotherapy, preferably in a neoadjuvant setting. Enlarged lymph nodes should be biopsied prior to surgery, and if positive then intravenous chemotherapy should be administered, followed by surgery if no progression, as with bladder UCC.

Radiation plays a very small role in the treatment of UTUCC. Adjuvant radiotherapy may help limit local disease in a palliative setting. Although its role is limited, when combined with chemotherapy it may improve survival and disease-free survival^[93,94].

MANAGEMENT/SURVEILLANCE

Management principles of UTUCC are similar to that of bladder cancer. Low grade/low stage tumors may recur, but have a low likelihood of progression and high grade/high stage tumors are more aggressive and have a higher chance to metastasize. The challenge is identifying tumors as Ta low grade and ruling out CIS and more aggressive tumors^[95,96] as obtaining adequate tissue for diagnosis can be challenging. Surveillance after treatment of UTUCC comes with many options. Per the European Association

of Urology guidelines, low grade/stage tumors follow up should include cystoscopy every 3 mo for 1-2 years with periodic urine cytology, then every 6 mo for 2 years^[41]. If renal sparing surgery was performed, an ureteroscopy would also be required. If the tumor was high grade/stage the management would be similar to that of the low grade/stage. In addition you would recommend imaging of the pelvis and abdomen and a chest X-ray.

CONCLUSION

Upper tract urothelial cell carcinoma is a rare disease with an incidence of less than 40000 cases per year. The most common presenting symptoms of UTUCC include hematuria and ureteral obstructive symptoms such as flank pain. The work up would then include cystoscopy, urine cytology, BUN, Creatinine and a CT Urogram. Tumor stage and grade are the most important prognostic factors to help the physician determine the best treatment options for the patient. Nephroureterectomy continues to be the gold standard for treatment in high grade, high stage tumors. In patients with low grade/stage disease, an absent contralateral kidney, poor renal function, or bilateral disease, renal sparing therapies including endoscopic resection, intravesical therapy with BCG or mitomycin C, and ureteral resection with ureteroureterostomy or re-implantation should be considered as an option for treatment. With appropriate treatment, the 5 year recurrence free survival rate for low grade/stage disease can be as high as 92%. However if the disease is not caught early and the patient has high grade/stage disease the 5 year recurrence free survival can be as low as 5%-48%. Factors such as high pathological stage, lymph node metastasis and vascular invasion increase the risk of recurrence and lead to decreased overall survival. Due to the aggressive nature of this disease, and lack of large prospective studies on this topic, large multi-institutional clinical trials are necessary to further investigate options for diagnosis, treatment, and surveillance to help those diagnosed with UTUCC.

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