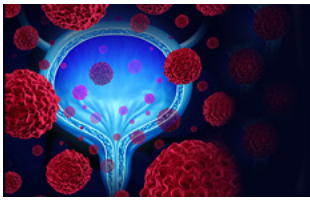

Addressing Challenges in Diagnosis and Treatment of Low-Grade Upper Tract Urothelial Carcinoma

CLINICAL INSIGHT

1. Introduction

Upper tract urothelial carcinoma, or UTUC, constitutes about 7% of all renal tumors and it constitutes up to 10% of urothelial carcinomas. Similar to bladder cancer, there's a male preponderance, with a 2:1 male:female ratio. UTUC is a disease of older patients, with a mean age at diagnosis of 73 years. About one-quarter of patients will have concurrent asynchronous bladder cancer and 22%–47% metachronous bladder cancer, with most of those occurring within 2 years. So, when we get to talking about surveillance, that time frame really is critical.

Upper tract urothelial carcinoma constitutes up to 7% of all renal cancers, with risk factors and etiology quite similar to bladder cancer

The risk of a contralateral UTUC, which is a second primary tumor of the upper urinary tract, is about 2%–5%. Patients with Lynch syndrome are at much higher risk for a contralateral tumor or bilateral tumors, whether they're synchronous or metachronous.

The risk factors and etiology of UTUC are quite similar to bladder cancer, with cigarette smoking the most common. Other risk factors include occupational risks such as diesel exhaust and aromatic amines. Although many patients are asymptomatic, hematuria is the most common symptom by far. Flank pain is also common, particularly if there's any component of obstruction.

2. Diagnosis

The Amsterdam II Criteria are used to identify patients with Lynch syndrome. Patients with Lynch syndrome have a 22-fold increased risk of UTUC compared with the general population. Lynch syndrome is relatively easy to identify using immunohistochemistry testing of ureteral or renopelvic tumor tissue to detect the presence of mismatch repair gene alterations in the tumor. One of the reasons to rule in or rule out Lynch syndrome is that pembrolizumab is approved for these patients, independent of tumor type. Immunohistochemistry tests are MLH1, PMS2, MSH2, and MSH6. Germline mismatch repair gene alterations are seen in about 9% of patients with upper tract tumors compared with 1% of bladder cancers.

The CT urogram is the benchmark to make the diagnosis of UTUC. A filling defect, often in the lower pole infundibulum, is the classic finding. The CT urogram is useful to assess tumor size, number, and whether or not there's evidence of infiltration which would suggest a more locally advanced high-grade cancer. MRI urography also can be used, especially in patients with contrast allergy.

The ureteropyeloscope is most commonly used for diagnosis. If there is difficulty passing the ureteroscope, a stent can be placed. In conducting the ureteroscopy, it is important to obtain a good quality tissue sample for stratification of low- or high-grade risk. A variety of tools for biopsy is available, each with its own set of benefits and limitations. Biopsy is preferable for determination of grade because a low-grade appearance visually is not as accurate for determining grade. In fact, upgrading the tumor occurs in about 20% of patients where the grade has been established visually. However, visual appearance can provide useful information about the tumor, such as whether it is sessile or papillary, large or small.

Biopsy is preferable to visual inspection for determination of disease grade

From a histopathologic perspective, UTUC is almost exclusively pure urothelial in nature, although variant histology may be seen, similar to what is observed in the lower urinary tract. The most common variant is squamous cell, generally indicating high-grade UTUC. In terms of cytology, a wash or barbotage sample is better than a voided sample since false negatives are common with a voided sample.

Several enhanced endoscopic imaging procedures have been or are being developed. These include fluorescence cystoscopy, narrow-band imaging, optical coherence tomography, and confocal microscopy. Since these have been developed for the lower urinary tract, they should not be considered standard of care at this point.

3. Surgical Treatment

Conventional treatment for UTUC is surgical, specifically radical nephroureterectomy, with complete removal of the intramural ureter. It's the standard of care for high-grade disease in the proximal ureter in the pelvis. Nephron-sparing surgery is an important treatment option, particularly for patients who are likely to have diminished glomerular filtration rate. Nephron-sparing surgery can be approached endoscopically, either through a retrograde or a percutaneous approach. Determination of partial or subtotal ureterectomies is determined by tumor location.

A 2014 meta-analysis showed no difference between radical nephroureterectomy and endoscopic surgery in overall survival or cancer-specific survival. The analysis also showed that local recurrence rates and bladder recurrence rates with the 2 techniques were quite similar. These findings must be interpreted cautiously since the level of evidence was low (3b).

Guidelines developed by the European Association of Urology in 2021 recommend nephron-sparing management:

- as primary treatment option for patients with low-risk UTUC
- specifically distal ureterectomy, for patients with high risk UTUC limited to the distal ureter
- for patients with solitary kidney and/or renal function, providing that it will not compromise survival, as determined through consultation with the patient

Imperative indications for nephron-sparing surgery might include patients with low-risk UTUC, solitary kidney, impaired renal function such as chronic kidney disease, bilateral disease, or comorbidities that pose a high surgical risk. Elective indications include low-grade UTUC, small volume, high-grade distal ureter disease, complete response to neoadjuvant systemic chemotherapy, or where there is a risk of upstaging by delaying radical nephroureterectomy.

In terms of postoperative treatment, there is level 1 evidence from 2 randomized trials supporting single-dosage investigational intravesical chemotherapy after radical nephrouterectomy, one utilizing mitomycin and the other pirarubicin. More recently, single-dose gemcitabine as investigational therapy showed a clear benefit in reducing the risk of recurrence as a single dose for patients with low-grade bladder cancer. This has prompted some clinicians to switch to gemcitabine to avoid potential toxicities with mitomycin such as necrosis of perivesical tissues if leakage occurs. Gemcitabine is generally retained for about an hour and is followed by catheter removal.

Recommendations regarding postoperative surveillance were included in the 2021 European Association of Urology (EAU) Guidelines, although the evidence for the recommendations was weak. Using a common-sense approach to surveillance, scoping patients at 4, 8, and 12 months, twice in year 2, and then annually for a little while longer depending on the individual patient may be reasonable.

Postoperative surveillance should follow a 'common-sense' approach

Imaging the upper tract is important, particularly the ipsilateral kidney in patients who have undergone nephron-sparing surgery. Monitoring the contralateral kidney is especially important in patients with Lynch syndrome.

4. Intracavitary Treatment

Intracavitary therapy for UTUC has been used for more than 30 years to deliver medication directly into the upper urinary tract. A variety of drugs have been used investigationally for intracavitary therapy, including mitomycin C, epirubicin, thiotepa, and Bacillus Calmette-Guerin vaccine (BCG) either alone or with interferon. Some evidence indicates better outcomes are achieved when intracavitary treatment is used for curative intent rather than as adjuvant therapy. A more contemporary meta-analysis concluded that there was no difference in outcomes with or without treatment, regardless of drug, stage/grade, delivery (percutaneous vs retrograde). Thus, there isn't a lot of high-level evidence to support intracavitary therapy with these treatment options. Intracavitary therapy may be considered in patients with high-grade disease since they are not eligible for treatment with mitomycin for pyelocaliceal solution, which was recently approved by the US Food and Drug Administration for patients with low-grade UTUC.

Mitomycin for pyelocalyceal solution is formulated with reverse thermal properties that appears as a viscous liquid for instillation. The safety and efficacy of mitomycin for pyelocalyceal solution were investigated in the prospective, phase 3, single-arm, open-label OLYMPUS trial. The trial involved patients with biopsy-proven, low-grade UTUC and no cytologic evidence of high-grade disease. Patients were treated once a week for 6 weeks followed by ureteroscopy 4–6 weeks later. Patients with no visible evidence of disease were evaluated by cytology, while patients with any abnormality were biopsied. At the follow-up evaluation, 59% of patients had a complete response, defined as a negative ureteroscopic evaluation, negative cytology, and negative for-cause biopsy (Table). Ongoing follow-up has demonstrated the complete response is durable with 82% maintaining a complete response at 12 months after the 4–6-week follow-up evaluation.

Table. Intention-to-treat analysis; N=71

Response	N (%)
Complete response	42 (59)
Partial response	8 (11)
No response	12 (17)
High grade	6 (9)
Indeterminate	3 (4)
Unresectable at baseline	20 (59)

Among adverse events, the most frequent was ureteral stenosis, which occurred in 44%. Other common adverse events included urinary tract infection (32%), hematuria (31%), flank pain (30%), and nausea (24%).