Endoscopic Approaches to Upper Tract Urothelial Carcinoma

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KEYWORDS

• Endoscopy • Ureteroscopy • Ureteral cancer • Laser • Upper-tract urothelial carcinoma

KEY POINTS

- All data supporting endoscopic management of upper-tract urothelial carcinoma are based on level 3 evidence, with no prospective studies available.
- Endoscopic management can be performed retrograde by ureteroscopy, or antegrade by percutaneous ureteropyeloscopy, as indicated.
- A variety of tools are available for tumor sampling and resection; although most of these were developed for treatment of stone disease, they can be improvised by urologists to adequately biopsy and treat tumors.
- Topical therapy may help reduce recurrences, but newer paradigms that are being prospectively tested may hold greater promise for efficacious treatment.
- Surveillance of the upper tract and bladder is mandatory after endoscopic management.

Video content accompanies this article at http://www.urologic.theclinics.com.

INTRODUCTION

Upper urinary tract urothelial carcinoma (UTUC) is uncommon and accounts for only 5% to 10% of all urothelial carcinomas.[1] Traditionally, radical nephroureterectomy (RNU) was considered the standard of care for UTUC. With increasing experience and enhanced technology, endoscopy for UTUC has increasingly been used.[2] This article summarizes the evidence for endoscopic management of UTUC in conjunction with our experience, highlighting the indications for its use and pitfalls.

DIAGNOSIS OF UPPER-TRACT UROTHELIAL CARCINOMA

Endoscopic evaluation is critical for the initial diagnosis and risk stratification of UTUC. Data gathered during endoscopy are not only useful for diagnosis of UTUC but also for prognosis and treatment planning, providing assessment for multilocality, multifocality, tumor architecture, and tumor biopsy, all highly relevant factors when determining an optimal treatment plan.

Urine-Based Studies

Positive cytology after a negative cystoscopic examination may be the first sign of UTUC.[2] However, cytologic examination of voided urine has poor sensitivity in detecting the rare malignant exfoliated cells from UTUC. Furthermore, false-positive rates caused by instrumentation effects and/or incidental inflammatory processes may be as high as 50%.[3] Site-directed collection via

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endoscopic measures (selective washings) have been shown to increase sensitivity for the detection of both high-grade (69% sensitivity, 85% positive predictive value [PPV]) and muscle-invasive UTUC (76% sensitivity, 89% PPV). Nevertheless, cytology alone may not be sufficient to predict pathologic findings of high-grade or muscle-invasive UTUC.[4]

In contrast, cytology can compensate for nondiagnostic or ambiguous endoscopic biopsy results. Kleinmann and colleagues[5] showed that diagnosis can be made by cytologic evaluation in almost all (91%) patients with nondiagnostic endoscopic biopsies. Furthermore, in patients with grade 2 tumors found on endoscopic biopsy, concomitant positive cytology increased the risk of upgrading[6] and upstaging to muscle-invasive UTUC[7] on RNU pathology. In patients managed with ureteroscopic laser ablation, abnormal cytology pretreatment also portended increased risk of recurrence (94.1% vs 47.1%; $P = .0026$).[8] Cytology from selective washings may also be the only indication for upper-tract carcinoma in situ (UTCIS), if no tumors are seen on a high-quality ureteroscopic evaluation.

Fluorescent in situ hybridization (FISH), a urine-based cytogenetic analysis, has also been used to diagnose UTUC. Compared with cytology, FISH consistently showed superior sensitivity (77%–100%) while maintaining comparable specificity in detecting UTUC on both voided[9] and selective washings.[10] In a multicenter study using selective washings, a group from Italy was able to achieve 100% sensitivity in detecting UTUC in 21 patients.[10] However, for UTUC, a high sensitivity would translate to a significant number of potentially negative ureteroscopic evaluations, which are more invasive than cystoscopy. Whether FISH can be used to reliably rule out UTUC requires validation in larger studies.

Ureteroscopy and Biopsy

Owing to difficult access and limited tissue samples, ureteroscopy (URS) biopsy of UTUC can be extremely challenging. In an attempt to obviate biopsy, many studies have assessed the adequacy of morphologic evaluation by URS inspection in predicting pathologic grading. The available evidence suggests gross underestimation of the tumor grading by endoscopic inspection, underscoring the importance of histology.[11,12] However, the visual architecture of tumors has been found to have strong predictive ability. Sessile-appearing tumors are consistently found to be associated with high-stage disease.[7,11]

In addition to increasing diagnostic accuracy, diagnostic URS with biopsy was found to shift management of UTUC toward less morbid options. Use of RNU was reduced by 20%, with only 5 URS needed to downgrade 1 patient from planned RNU to organ-sparing management. The investigators were careful to point out several scenarios in which URS evaluation may be avoided: (1) nonfunctioning kidney; (2) history of ipsilateral UTUC; (3) positive cytology with multifocal lesions on imaging. In each of these cases the investigators suggest avoiding URS and proceeding with RNU. A fourth scenario, a positive biopsy of a regional lymph node, would indicate the need for chemotherapy as initial primary therapy.

A few concerns regarding the routine use of URS biopsy have been allayed. Kulp and Bagley[13] addressed the fear of metastatic spread via pyelovenous and pyelolymphatic backflow by examining the surgical specimens from RNU. On histologic examination, no free-floating tumor cells were found in the vascular or lymphatic spaces of the submucosa or renal parenchyma surrounding the tumor. In a subsequent clinical study, Hendin and colleagues[14] showed the lack of difference in metastasis rates after RNU in patients receiving preoperative URS with a variety of irrigation systems versus those who did not. A second concern is possible bladder implantation by sloughed UTUC cells during URS leading to increased intravesical recurrences. Although Ishikawa and colleagues[15] found similar rates of intravesical recurrence in patients with or without preoperative URS (60% vs 59%; $P = .9$), others described a higher incidence of intravesical recurrence in patients having undergone URS (hazard ratio, 1.44–2.58).[16] The use of perioperative intravesical chemotherapy has been adopted after RNU to reduce intravesical recurrence, but the utility in the setting of diagnostic URS has not been investigated. A third concern pertains to the delay in definitive treatment, which has previously been linked to numerous adverse pathologic features such as advanced stage, grade, and lymphovascular invasion (LVI), as well as increased disease recurrence and cancer-specific mortality.[17] However, the interval from diagnosis on imaging to RNU caused by diagnostic URS has not been found to impair cancer-specific survival, recurrence-free survival, or metastasis-free survival.[18]

Drawing from their extensive experience, Tawfiek and colleagues[19] first described detailed methods of ureteroscopic inspection and biopsy. Emphasis was placed on obtaining multiple urine and washing samples before and after biopsy. Subsequently, Guarnizo and colleagues[20] also