Review Article on Upper-Tract Urothelial Carcinoma: Current State and Future Directions

Ureteroscopic biopsy of upper tract urothelial carcinoma and role of urinary biomarkers

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Abstract: Ureteroscopic biopsy is an integral part of diagnosis of urothelial carcinoma of the upper urinary tract. It can be a technical challenge, but diagnostic rates have improved remarkably with refinements in surgical technique and specimen processing. Cytology aids with diagnosis and other urinary biomarkers continue to evolve, which may help further stratify patients for treatment. The current literature on the ureteroscopic biopsy and role of urinary biomarkers is reviewed and summarized below.

Keywords: Upper tract urothelial carcinoma (UTUC); ureteroscopy; biopsy; urinary biomarker

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Introduction

Significant advancements have been made in the last 30 years in the diagnosis of upper tract urothelial carcinoma (UTUC), but certain aspects still remain a challenge for the clinician. Computerized tomographic urography (CTU) has made great strides in aiding the diagnosis of urothelial malignancies with 88–100% sensitivity and 93–100% specificity on meta-analysis (1). Additionally, it can detect filling defects as small as 5 mm (2). A major barrier is that imaging alone fails to provide tissue diagnosis to guide further treatment. It therefore remains part of the work-up, rather than a means for definitive diagnosis. Repeated radiation exposure also remains a concern (1).

Currently, ureteroscopy with biopsy is the cornerstone of initial diagnosis and ongoing surveillance (3,4). Using our method of diagnosis and specimen handling, we have achieved a 97.2% success rate in grading biopsy specimens, mainly by changing the way we process specimens (5). Despite this, ureteroscopy also has its limitations, which will be described herein.

All of the above highlight the need for the development of a non-invasive means for diagnosis. The role of urinary biomarkers has been an interest of study as a method to aid diagnosis and surveillance after treatment without need for radiation or ureteroscopy and general anesthesia. Cytology is the most widely utilized. Improved diagnostic correlation has recently been suggested with introduction of the Paris System for urine cytology (6,7). Other options, such as FISH have been discussed previously. Currently the detection of DNA mutations and methylation markers in voided urine has gained some popularity in the literature, and preliminary analysis shows promise as a biomarker in the detection of UTUC.

Methods

A literature review was performed by searching PubMed and Google Scholar using relevant keywords. Results were screened for pertinent publications, with a focus placed on publications from the last 10 years. Further references were obtained from the citations of these papers, as well as guidelines and textbooks.

Ureteroscopic biopsy

We have reported notable success with ureteroscopic biopsy as described above, and other studies have reported similar success with a sensitivity and specificity of 83% and 100% respectively (8). Arguments have been made for the avoidance of ureteroscopy and biopsy in cases of positive urine cytology and an obvious lesion on CTU when the added diagnostic benefit will not affect management (9). However, in many cases, the outcome of ureteroscopy and biopsy will direct potential neoadjuvant chemotherapy or nephron-sparing treatments and is therefore beneficial. Below we describe our method of ureteroscopic biopsy (10,11).

Initial approach and surveillance

Evaluation for upper tract urothelial cancer should always begin with thorough cystoscopy of the bladder to rule out concomitant bladder tumors. Urine cytology from the bladder is then obtained and bilateral retrograde pyelograms are performed with great care to avoid excessive back pressure and extravasation. Retrograde pyelogram sets the stage for what to expect. The index of suspicion for encountering an upper tract lesion will be high if a filling defect or stricture is demonstrated.

Ureteroscopic examination of the affected side commences with "no touch" technique. Via this method, manipulation of the urothelium is minimized as not to induce mucosal trauma or bleeding, which could impair detection of subtle lesions. Traditionally, a small semi-rigid ureteroscope is used to examine the distal ureter under direct vision. No wire is passed prior to ureteroscopy and the ureteral orifice is ideally entered without the use of dilation. The ureteroscope is then passed as proximally as possible and replaced with a guidewire, which is not advanced beyond the proximal extent of ureteroscopic examination. The smallest flexible ureteroscope available is then passed over the wire to this point. The remainder of the ureter is examined, and complete ureterorenoscopy is performed in a systematic manner from the upper pole to lower pole, to ensure direct examination of all the potential space of the intraluminal collecting system. If ureteral tumors are encountered during initial ureteroscopy, these are biopsied and treated at the time of discovery. Performance of upper urinary tract surveillance with the exclusive use of flexible ureteroscopy is now possible with the development of optimal distal shaft durometer (shaft stiffness), making semi-rigid instruments necessary in only about half of all cases (12).

Biopsy technique

When a lesion is encountered, cytology washings are taken via the irrigation channel of the ureteroscope. Then biopsy can be performed using a variety of methods, including 3-F cold cup forceps (Piranha), 6-F back loading biopsy forceps (BIGopsy), or ureteroscopic basket. Several studies have compared these options and noted a 74.9–79% diagnostic rate for 3-F cold cup forceps, 81.9–90% for BIGopsy and 87–100% when using a 2.2-F or 2.4-F wire basket (13,14). In our practice, we favor 3-F cold cup forceps or a 2.4-F stainless steel FlatWire basket (*Figure 1*). We find BIGopsy forceps impractical due to its back loading nature, tendency to obscure the field of view, and its severe limitations on ureteroscopic deflection (15). Our choice of cold cup forceps versus basket depends on the nature of the lesion; with the cold cup biopsy forceps being superior for sessile lesions, while the stainless steel basket is useful for large friable tumors. We have found that when suitable, the FlatWire basket obtains superior diagnostic results (16). Relatively large volumes of tumor can be sampled (*Figure 2*). It is the opinion of the authors that stainless steel FlatWire baskets are superior to nitinol baskets for luminal tissue biopsy. Relative to the round, soft wires which comprise nitinol baskets, the flat wires of the stainless steel basket are more rigid and superior in grasping and holding tissue in the angle between the wires with flat edges, allowing for better tissue sampling.

Once the biopsy is obtained, the tumor sample, biopsy device and ureteroscope are removed together as one unit, in order to avoid shearing and loss of the sample. Following this, aspiration for cytology is repeated. If the lesion is endoscopically treated, a final cytology is taken following treatment.

Specimen processing

All specimens in our practice are sent to cytopathology and processed using the Cytospin technique (10). Any viable tissue is prepared using a cell block. We developed this method as we found that ureteroscopy specimens processed as traditional histological specimens were destroyed during processing. By sending these tumor samples as cytology, diagnostic yield improved from 42.9% to 97.2% (5). Similarly, when Vashistha *et al.* examined the accuracy of

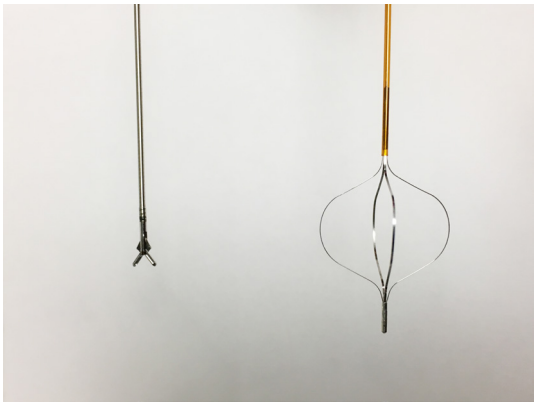

Figure 1 Instruments for ureteroscopic biopsy of upper tract urothelial carcinoma: 3-F cup biopsy forceps (left) and 2.4-F stainless steel flatwire basket.

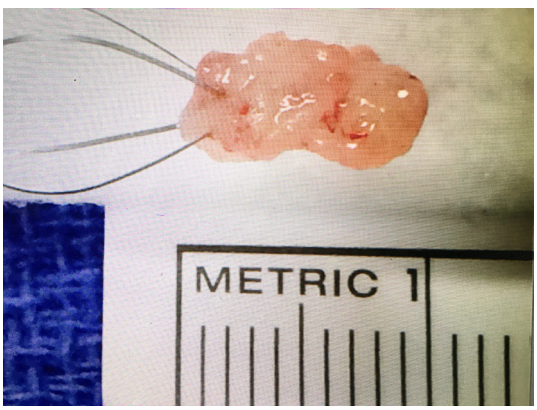

Figure 2 Relatively large luminal tissue samples can be obtained with good endoscopic visualization and preservation of flexible ureteroscope deflection using the 2.4-F stainless steel FlatWire basket. Note the tumor tissue caught in the notch between the flat wires.

ureteroscopy biopsy in 118 samples, specificity was 100% and sensitivity was 83.0% (8). Specimen processing was not overtly addressed, however it was implied that biopsies underwent traditional histological preparation.

Limitations

Despite these successes, ureteroscopic biopsy still remains an imperfect technique in that staging is notoriously inaccurate. Despite the aforementioned specificity and sensitivity, Vashistha found disappointing stage concordance between biopsy specimen and final pathology of 58.6% (8). Therefore, tumor grade remains the guiding force in treatment decisions (3,4).

Given these limitations, efforts have been made to identify patients at risk for muscle invasive disease. Margolin *et al.* found that patients with clinical high grade tumors on ureteroscopic biopsy were found to have a 60% positive predictive value (PPV) for muscle invasion. If subepithelial tissue was captured on biopsy and was positive, this increased the PPV to 86% (17).

Other avenues of diagnosis have been explored, such as percutaneous biopsy. In a study looking at 26 patients who underwent percutaneous biopsy for a variety of indications (nondiagnostic URS, prior cystectomy or poor surgical candidate), successful diagnosis of urothelial carcinoma was made in 85% of cases. However similar to ureteroscopic biopsy, the ability for staging remains limited. In the same study, 14/24 patients had grade information available and 86% demonstrated concordance with final pathology. Despite diagnostic rates that are comparable to URS and biopsy, percutaneous access comes with the risk of tumor seeding. In the aforementioned study, 13% of patients demonstrated local recurrence. However, this was determined as unrelated to biopsy as the tumor recurrence was outside of the needle tract. There is, however, literature that supports the risk of tumor seeding, predominantly with percutaneous resection and laparoscopic intervention (18).

Urinary biomarkers

The use of urinary biomarkers is an invaluable adjunct to diagnosis, with cytology being the most popular, despite its flaws. Cytology does not always provide a clear diagnostic picture, and often times ureteroscopy is needed to further characterize a lesion prior to intervention, which results in several issues. Firstly, not only is ureteroscopy often needed for initial diagnosis, but if a lesion is found, it may subject patients to a need for repeated ureteroscopic surveillance. This results in increased fluoroscopic exposure as well as repeated general anesthesia. Secondly, data has remained mixed on whether diagnostic URS increases the risk of intravesical recurrence of urothelial carcinoma (19,20). A meta-analysis by Guo *et al.*, which looked at 8 studies including 3975 patients, found that those who undergo diagnostic URS are at higher risk of intravesical recurrence however this did not negatively impact survival parameters (21). The field of biomarker development for diagnosis and monitoring therefore remains a continued area of interest.

Table 1 Diagnostic categories described by the Paris system

Nondiagnostic/unsatisfactory
Negative for high-grade urothelial carcinoma (NHGUC)
Atypical urothelial cells (AUC)
Suspicious for high-grade urothelial carcinoma (SHGUC)
High-grade urothelial carcinoma (HGUC)
Low-grade urothelial neoplasm (LGUN)
Other: primary and secondary malignancies and miscellaneous lesions

Cytology

Although cytology remains a gold standard diagnostic tool for UTUC, voided cytology is notoriously inaccurate, with false negative rates of 50–89% (22,23). Selective cytology has demonstrated greater diagnostic accuracy with meta-analysis revealing a 53.1% sensitivity with 90% specificity based on biopsy. Sensitivity is highest for high grade at 70% but notably lower for low grade (46%). Part of this ambiguity arises from the great variability in how cellular "atypia" is characterized and the notoriously poor inter-and intraobserver agreement in grading urine cytology (22,24).

To solve the latter problem, new methods of cytologic grading have been developed. The "Paris System" was first described in the literature in 2016 as a new classification method that uses specific criteria in an effort to increase diagnostic accuracy and focuses mainly on high grade diagnosis (24). *Table 1* describes the different categories set forth by this system. Studies have shown a 71–78.6% sensitivity and 86–100% specificity rate and an almost double rate of surgical concordance when compared with traditional cytology in upper tract disease (63% compared to 34%) (6,7,25). The false negative rate was reported as 7% and attributed to sampling errors, compared to historical rates of 26% (6). McIntire *et al.* also found that implementing the Paris System decreased equivocal or atypical diagnoses by 55%. However, Xing *et al.*, as well as Simon *et al.*, reported a decrease in sensitivity when compared to traditional cytology (7,25,26). Therefore, controversy still remains, as does the ongoing issue of detecting low grade disease.

Fluorescence in situ hybridization testing (FISH)

FISH testing uses fluorescent probes to detect abnormalities in chromosomes 3, 7, 17 and 9p21 (27). While popular as an adjunct to bladder cancer diagnosis, efforts have been made to apply FISH to UTUC with inconsistent results. When applied to voided urine without concomitant bladder tumor, sensitivity and specificity has varied widely, and reported at 54–76.7% and 78–94.7% respectively (28,29).

DNA methylation biomarkers

The role of epigenetic changes in cancer has been increasingly recognized. Based off tissue immunology, the methylation status of multiple genes has been shown to be associated with UTUC and this work has been extrapolated to the development of urinary biomarkers. Two studies looked at the diagnosis of UTUC by examining voided samples for *GDF15*, *TMEFF2* and *VIM* promoter methylation status. Monteiro-Reis *et al*. looked at 22 patients with known UTUC and found that this panel detected UTUC with 91% sensitivity. UTUC samples demonstrated a significantly higher degree of methylation and this was used to calibrate levels to controls, resulting in a specificity of 100%. Furthermore, *VIM* methylation status independently was associated with stage and low *VIM* methylation levels were associated with poor disease-specific survival. It should be noted that only 3 patients had low grade UTUC and no analysis was performed to look at accuracy of diagnosis in these samples (30). Similarly, Guo *et al*. examined a similar panel, with the addition of genes CDH1, HSPA2 and RASSF1A with a notably lower sensitivity of 82% and specificity of 68%. Neither of these studies examined whether methylation could distinguish between lower and upper tract lesions (31).

Gene mutation biomarkers

Several gene mutations have been associated with urothelial carcinoma, and efforts have been made to identify urinary assays that would identify these abnormalities. Hotspot mutations in telomerase reverse transcriptase (*TERT*) have been investigated as a possible target as well as *FGFR3*. When examining *TERT* and *FGFR3* mutations in conjunction with cytology had a sensitivity of 78.6% and specificity of 96% (32).

Miscellaneous

Other tumor markers have been described for upper tract

detection over the past 20 years such as the BTA stat test, FDP test, nuclear matrix protein 22 (NMP 22), and ImmunoCyt (11). Despite sometimes promising results, they have failed to achieve mainstream or guideline endorsed use.

Conclusions

Ureteroscopy with biopsy in conjunction with urinary markers has greatly increased our ability to detect and diagnose UTUC, however barriers remain. Great strides have been made with the improvement in endoscopic techniques for UTUC diagnosis and specimen handling which have improved diagnostic accuracy. There is an ongoing challenge in the use of urinary cytology, but with improvements and standardization in specimen interpretation, this may improve. Similarly, the role of DNA markers in the role of diagnosis remains experimental but holds promise to increase future diagnostic capabilities in UTUC. Further large volume and prospective studies are still needed in order to determine the best means of non-invasive UTUC diagnosis.

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Footnote

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