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Low biopsy volume in ureteroscopy does not affect tumor biopsy grading in upper tract urothelial carcinoma

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Abstract

Objectives: Urothelial carcinomas (UC) from the upper urinary tract represent 7%–10% of all kidney malignancies. With current ureteroscopic (URS) techniques, small tissue samples are usually the only available histopathologic material for evaluation, representing a diagnostic challenge. Precision in diagnosis is essential for treatment decision making. There has been much debate as to whether tumor grade and stage found on biopsy agree with final pathology. The purpose of this study is to evaluate whether URS biopsy volume affects tumor grading and staging agreement between biopsy and nephroureterectomy (NU) specimens.

Materials and methods: We reviewed 137 URS biopsies in 81 patients with suspected upper urinary tract UC performed from April 2002 to April 2011. Of those, 54 patients had both the URS biopsy and NU performed at our institution and were available for review. Biopsy dimensions were recorded to calculate estimated ellipsoid volume, and 2 urological pathologists independently evaluated histologic grade (ISUP/WHO 2004), (based on pleomorphism and mitosis) and depth of invasion. Statistical analysis was performed to evaluate URS biopsy and NU specimen grade and stage concordance. In addition, univariable and multivariable analyses was performed to assess the effect of biopsy volume on agreement.

Results: Of the 54 patients studied, low grade and high grade UC biopsy were found in 8 (15%) and 46 (85%), URS biopsies, respectively. Regarding biopsy stage, 51 (94%), 1 (2%), and 2 (4%) were stage Ta, T1, T2, respectively. Grade concordance was 92.6%, (95% CI: 82.4%–98.0%). Stage concordance was 43% (95% CI: 28.7%–55.9%). Multivariable analysis showed biopsy volume did not affect tumor assessment of grade ($P = 0.81$) or stage ($P = 0.44$).

Conclusions: Histologic grade assigned on the URS biopsy sample accurately predicts histologic grade in the resected specimen (92.6%), even when the biopsy volume is small. Grading in URS biopsies provides sufficient information for clinical decision making that is independent of sample volume.

Keywords: Upper urinary tract; Urothelial carcinoma; Ureteroscopy; Nephroureterectomy

1. Introduction

Upper tract urothelial carcinoma (UC) is estimated to represent <10% of renal tumors and accounts for 5% of all UC [1]. Recent evidence indicates that the frequency of upper urinary tract malignancies is increasing [2].

Historically, radiographic imaging has been used to evaluate upper urinary tract lesions, including contrasted CT

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scan, and intravenous and retrograde pyelography. However, direct inspection of the urinary tract via ureteroscopy (URS) with concomitant biopsy has proven to have the highest diagnostic sensitivity [3]. The URS approach is typically the least invasive surgical treatment option, and the best initial method for procuring an adequate tissue sample for diagnosis and grading [4]. Nephroureterectomy (NU) remains the gold standard for treatment of upper tract UC, and produces an improved survival for those patients [5,6]. However, for those patients with low grade UC of the distal ureter, distal ureterectomy and ureteroneocystostomy may be performed.

Histologic grade and tumor stage are well established prognostic factors of UC [4,5,7]. The histologic grade is determined by cellular pleomorphism and the presence of mitosis. In addition, histologic grade has been closely associated with tumor stage [4,7,8]. Lymphovascular invasion has also been identified as a poor prognostic factor but is difficult to evaluate in biopsy samples [7,9]. Based on these histologic results, treatment modalities may vary from observation, endoscopic management, or nephroureterectomy (NU).

There has been current debate on whether URS biopsy provides an accurate diagnosis for upper tract UC grade [10–12]. A potential pitfall of the URS biopsy is insufficient tissue sampling. Small volume of biopsy material may display a limited number of malignant cells, potentially compromising an accurate histologic grade. Furthermore, a reliable full thickness sample may not be available to accurately diagnose the presence of muscle invasion. This is due to the relatively thin ureteral wall and the associated risk of perforation if deep biopsies are attempted. Also, the diameter of the working channel of current ureteroscopes is $<$1/3 mm, making biopsy forceps delicate and small in diameter. Therefore, the volume of the tissue samples obtained may be limited, becoming a challenge for the pathologist when assessing histologic grade and depth of invasion. Additionally, for some lesion locations, it may be difficult to obtain a biopsy; therefore, URS biopsy of all suspected upper tract UC is not ubiquitous among urologists, and NU may be performed without a tissue diagnosis. However, there is an inherent risk of end-stage renal disease in these patients undergoing kidney removal, and a risk of increased comorbidity and mortality [13]. Therefore, pathologic diagnosis is of utmost importance to appropriately treat patients while preserving renal function if possible.

We wished to investigate whether the URS biopsy volume of upper tract UC lesion affected the agreement between URS biopsy and NU specimens in terms of tumor stage, grade, and histopathologic parameters. Our goal is to determine whether URS biopsies should be attempted in lesions that may result in small volume samples, and whether this will affect the pathologist's ability to grade and stage the tumor. To our knowledge, there are no studies that correlate the biopsy sample size with the final pathology of NU specimens.

2. Materials and methods

We reviewed all URS biopsies performed from April 2002 through April 2011 for suspected upper tract UC. A total of 137 biopsies were performed in 81 patients (multiple biopsies in some patients). Of those 81 patients, 54 underwent both their URS biopsy and NU at our institution and had histopathology available for review from both specimens. Tissues from both procedures were evaluated. If the patient had multiple biopsies at different times, only the biopsy directly preceeding NU was evaluated since the decision to perform NU was based most strongly on this biopsy result.

At our institution, URS biopsy is recommended to all patients with an upper tract mass suspicious for UC with no prior histopathologic diagnosis. NU is offered to all patients with an upper tract urothelial tumor, and recommended to patients with high grade invasive disease or low grade tumors that are multifocal, high volume, or rapidly recurring. Endoscopic management is recommended to patients with low grade, low-stage disease. Pathologic diagnosis from URS biopsy is factored into therapy choice (observation, endoscopic management, or NU) along with the risks of chronic kidney disease and patient comorbidities. Ultimately, patients make the decision whether to receive NU based on recommendations provided by the surgeon.

2.1. Ureteroscopic biopsy

All URS biopsies were performed by 2 experienced, fellowship trained endourologists. Retrograde pyelograms were routinely evaluated before URS to further delineate the anatomy. Piranha forceps (Boston Scientific Corp., Natick, MA) and/or Segura basket (Boston Scientific, Corp., Spencer, IN) were commonly used through a flexible or semirigid ureteroscope. For those tumors unable to be accessed via rigid or semirigid URS, a flexible ureteroscope was used along with a ureteral access sheath to facilitate reintroduction of the ureteroscope. Specimens were placed in formalin and immediately sent to the pathology laboratory.

2.2. Tissue processing and sample evaluation

Before tissue sectioning, 3 measurements of each sample (length, width, height) were recorded and used to approximate tissue volume using an elliptic formula ($4/3 \times \pi \times a \times b \times c$, a = length, b = width, c = height). Hematoxylin-eosin (H and E) staining was performed on formalin fixed-paraffin embedded tissue from URS biopsies and corresponding NU specimens. Two urological pathologists independently evaluated the following disease characteristics: histologic grade (pleomorphism, mitosis, according to WHO 2004 criteria), depth of invasion, and lymphovascular invasion (LVI) in both URS biopsies and NU specimens. In the case of disagreement between pathologists (2 cases), a