Ureteroscopic biopsy of upper tract urothelial carcinoma using a novel ureteroscopic biopsy forceps

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Introduction: *We sought to assess the adequacy of surgical specimens obtained utilizing the BIGopsy (Cook Medical, Bloomington, IN, USA) biopsy forceps both ex vivo and in vivo and compare them to traditional 3Fr biopsy forceps in patients with suspected upper tract urothelial carcinoma.*

Materials and methods: *Patients undergoing nephroureterectomy for suspected upper tract transitional cell carcinoma were recruited. Surgical specimens, immediately after extirpation were examined and alternatively biopsied ex vivo with the BIGopsy and 3Fr biopsy forceps. We then retrospectively reviewed our most recent experience with ureteroscopic biopsy. The biopsy device, size, depth, grade, stage, pathologic diagnosis and subjective biopsy quality were assessed.*

Results: *Three ex vivo nephroureterectomy specimens were evaluated. The average biopsy size from the 3Fr biopsy forceps was 3.5 +/- 2.8 mm^2 and for the BIGopsy was 31.2 +/- 34.6 mm^2. Subjectively, the BIGopsy specimens revealed less distortion and fragmentation and were easier to interpret by the pathologist. Sixteen patients underwent 19 ureteroscopic procedures. The mean size in maximal diameter (mm +/- SD) of the biopsies in each group were; 3Fr 1.2 +/- 0.4, BIGopsy 3.4 +/- 2.0, nitinol basket 4.9 +/- 4.0 and laser 11 +/- 8.5. Lamina propria was identified in 3/13 (23%) biopsies with 3Fr biopsy forceps, 6/11 (55%) biopsies with the BIGopsy forceps, 6/8 (75%) biopsies with the nitinol basket and 2/2 (100%) biopsies with the holmium laser. Six patients underwent biopsies with both the BIGopsy and 3Fr biopsy forceps. A definitive diagnosis was made in 2/6 cases with the 3Fr biopsy forceps compared with all 6/6 cases with the BIGopsy biopsy forceps. Grade and stage matched final surgical grade and stage in 3/3 cases biopsied with the BIGopsy.*

Conclusion: *For lesions with stalks, the holmium laser and basket biopsy provided larger specimens than either of the forceps. For flat or sessile lesions, the BIGopsy biopsy forceps provided larger, deeper less distorted specimens than the 3Fr biopsy forceps and correlated well with ultimate grade and stage. Improved biopsy quality may translate into improved ability to diagnose both benign and malignant ureteral and renal pelvic mucosal lesions endoscopically.*

Key Words: transitional cell cancer, ureteroscopy, instrumentation, biopsy

Introduction

Upper tract urothelial carcinoma (UUC) accounts for approximately 5% of all urothelial malignancies and evidence suggests that its incidence is on the rise.[1,2] These cancers are often associated with a poor prognosis.[3] UUC is highly lethal owing to its propensity to spread by direct parenchymal invasion, mucosal seeding, and by hematologic and lymphatic routes.[3,4] The evaluation of suspected UUC consists upper tract imaging, voided urinary cytology, selective upper tract cytology, cystoscopy, and retrograde pyelography.[5,6] This is accurate for establishing a diagnosis 50%-60% of the time.[7] Ureteropyeloscopy and biopsy increases this accuracy to 80%-90%.[7-10] Traditionally biopsy of suspicious lesions is carried out using 3Fr cold cup biopsy forceps (Pirhana, Boston Scientific, Natick, MA, USA).[11] Histologic correlation between ureteroscopic biopsy specimens and final pathologic specimens ranges from

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78%-92%.[7,12] Both tumor grade and tumor stage offer invaluable information for characterizing the biological aggressiveness of UUC and is often times underestimated by the biopsy at the time of ureteroscopy.[13] Guarnizo and colleagues reviewed their series of 40 urothelial tumors and found that ureteroscopic grade matched surgical grade in 32 cases, and therefore was underestimated in 22% of patients.[7] As higher grade tumors have a higher propensity for multifocality, invasion, and increasing tumor stage, accurate tumor grading on ureteroscopic biopsy is critical for patient management.[2]

Currently stage is the most important predictor of survival in patients with UUC.[3,14-16] Due to the small size of traditional ureteroscopic biopsy specimens, a precise correlation with eventual tumor stage is often difficult and may be underestimated in up to 50% of cases.[7,12,17] Guarnizo and colleagues found that approximately 45% of tumors thought to be Ta were upstaged to T1 to T3 at the time of complete resection.[7] Brown and colleagues had similar findings in their series of 119 patients in which 28.3% of patients with clinical grade 2 disease had a final pathologic stage of > pT2.[18] These studies suggest that the accuracy of preoperative staging may be improved with larger and deeper ureteroscopic biopsies.

The yield of standard 3Fr ureteroscopic biopsy forceps is limited by the diameter of the flexible ureteroscope working channel which has a 1 mm^3 biopsy head volume. The 2.4Fr BIGopsy biopsy forceps (Cook Medical, Bloomington, IN, USA) has a unique backloading design which allows the biopsy head to exceed the diameter of the working channel. The biopsy head is attached to a flexible wire that is backloaded through the working channel of the ureteroscope. Once the biopsy device is placed into the ureteroscope, the wire is connected to a handpiece which controls the opening and closing of the jaws. As a result of the backloading design, the biopsy head protrudes in front of the ureteroscope by several millimeters, requiring the use of a ureteral access sheath. Once a biopsy is obtained, the entire ureteroscope must be withdrawn for specimen retrieval.

Recognizing that small biopsies may preclude adequate pathologic evaluation, we sought to assess the adequacy of surgical specimens obtained with the BIGopsy biopsy forceps both ex vivo and in vivo and compare them to traditional 3Fr biopsy forceps. To our knowledge, no studies have been published directly comparing the two types of biopsy forceps. We hypothesize that the BIGopsy biopsy forceps will provide larger and deeper sample of urothelial tissue for examination and improve accuracy in pathologic interpretation.

Materials and methods

Ex vivo

In accordance with our Institutional Review Board, patients undergoing nephroureterectomy for upper tract transitional cell carcinoma were recruited. Surgical specimens, immediately after extirpation were examined and bivalved. The most clinically suspicious region to gross examination was alternatively biopsied with the 3Fr biopsy forcep, followed by the BIGopsy biopsy forcep, obtaining up to three biopsies with each device. Specimens were then immediately placed in saline, fixed, stained and evaluated by a single pathologist. Biopsy size, histopathologic diagnosis, grade, stage, depth of invasion and qualitative assessment were noted. Histopathologic diagnosis from the biopsy was compared with the final pathologic diagnosis of the surgical specimen.

In vivo

We retrospectively reviewed our most recent experience in ureteroscopic biopsy (2008-2010) in patients with suspected upper tract transitional cell carcinoma undergoing ureteroscopy and biopsy. Specimens obtained from ureteroscopy were immediately placed in saline and sent directly to pathology for immediate processing. They were then fixed, stained and evaluated by a single pathologist. The biopsy device, size, histopathologic diagnosis, grade, stage and depth were noted. The pathologist was blinded to cytology results. Histopathologic diagnosis from the biopsy was compared with the final pathologic diagnosis of the surgical specimen if it was available. Staging was based on the current American Joint Committee on Cancer (AJCC) TNM Clinical Classification for Renal Pelvis and Ureteral Tumors.[19]

Results

Ex vivo

Three nephroureterectomy specimens were evaluated. A total of six biopsies were obtained from the 3Fr biopsy forceps and 5 biopsies were obtained from the BIGopsy biopsy forceps. The size of the biopsies from the 3Fr biopsy forceps ranged from 1 mm^2-to 8mm^2, while those from the BIGopsy ranged from 6 mm^2 to 80 mm^2. The average biopsy size of the 3Fr biopsy forceps was 3.5 +/- 2.8 mm^2 while the average biopsy size of the BIGopsy was 31.2 +/- 34.6 mm^2. The difference was not statistically significant ($p = 0.08$). In two specimens, histopathologic diagnosis from the 3Fr biopsy specimens was pTa high grade papillary urothelial carcinoma, while the third was suspicious for

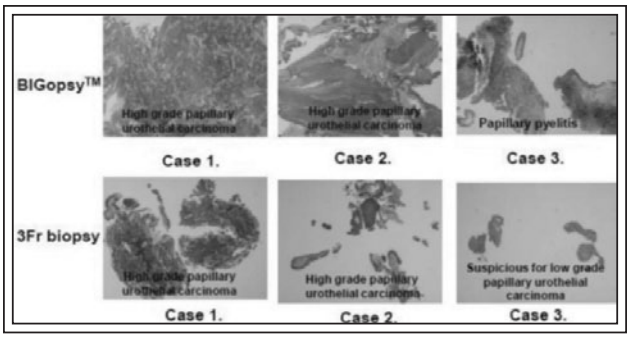

Figure 1. Representative photographs of BIGopsy versus 3Fr biopsy forceps. MAG 20x

a pTa low grade urothelial neoplasm. In two specimens, histopathologic diagnosis from the BIGopsy biopsy specimens was pTa high grade papillary urothelial carcinoma, while the third was benign polypoid/papillary pyelitis. In two of three nephroureterectomy specimens, the final pathologic diagnosis was pTa high grade papillary urothelial carcinoma in accordance with both the 3Fr biopsy and BIGopsy biopsy specimens. In the third nephroureterectomy specimen, the final pathologic diagnosis was pT0 benign polypoid/papillary pyelitis consistent with only the BIGopsy specimen. Subjectively, the BIGopsy biopsy specimens revealed less distortion and fragmentation and were easier to interpret by the pathologist, Figure 1. Smooth muscle was contained in one BIGopsy specimen and in none of the 3Fr biopsy specimens.

In vivo

Sixteen patients underwent 19 ureteroscopic procedures. Several biopsies were obtained using different devices in multiple patients. Average patient age (+/-SD) was 68 +/- 11 (range 41-91). There were 12 (75%) males and 4 (25%) females. Eight (50%) suspicious lesions were located in the renal pelvis, 6 (38%) were located in the ureter, while 2 (12%) were located in both the renal pelvis and ureter. Six (38%) patients had previously endoscopically visualized lesions, Table 1. Indications for ureteroscopy included 10 (63%) patients that had suspicious findings and/or filling defects on upper tract imaging and 13 (81%) patients with a history of abnormal cytology. Eleven (69%) patients underwent biopsy with 3Fr biopsy forceps and 9 (56%) patients underwent biopsy with the BIGopsy biopsy forceps. One (6%) patient had a lesion excised with the holmium laser and 6 (38%) patients underwent en bloc excision utilizing a nitinol basket to snare the stalk of the lesion. Lamina propria was identified in 3/13 (23%) biopsies with 3Fr biopsy forceps, 6/11 (55%) biopsies with the BIGopsy forceps, 6/8 (75%) biopsies with the nitinol basket and 2/2 (100%) biopsies with the holmium laser, Table 2. The mean size in maximal diameter (mm +/-SD) of the biopsies in each group were: 3Fr 1.2 +/- 0.4, BIGopsy 3.4+/- 2.0, nitinol basket 4.9+/- 4.0 and laser 11+/- 8.5, Figure 2.

Six patients underwent biopsies with both the 3Fr and BIGopsy™ biopsy forceps. Of those who underwent biopsy with both biopsy forceps the mean difference in size was 1.8 mm (p = 0.09). A definitive diagnosis was made in 2/6 cases with the 3Fr biopsy forceps compared with 6/6 cases with the BIGopsy biopsy forceps. The 3Fr biopsy forceps established a diagnosis of pyelitis

TABLE 1. **Demographic, clinical, and pathologic tumor characteristics of study cohort**

Characteristic	n (%)
Age	
Average	68 +/- 11
Range	41-91
Sex (n = 16)	
Men	12 (75%)
Women	4 (25%)
Tumor location (n = 16)	
Renal pelvis	8 (50%)
Ureter	6 (38%)
Renal pelvis and ureter	2 (12%)
Clinical grade (n = 14)	
Low grade	4 (29%)
High grade	4 (29%)
Benign urothelium	6 (43%)
Stage (n = 9)	
CIS	1 (11%)
Ta	7 (78%)
T1-4	1 (11%)

TABLE 2. **Number of specimens for each biopsy forcep where lamina propria was identified**

	Lamina propria identified	
	Yes	**No**
3Fr biopsy forceps	3 (23%)	10
BIGopsy forceps	6 (55%)	5
Nitinol basket	6 (75%)	2
Laser	2 (100%)	0

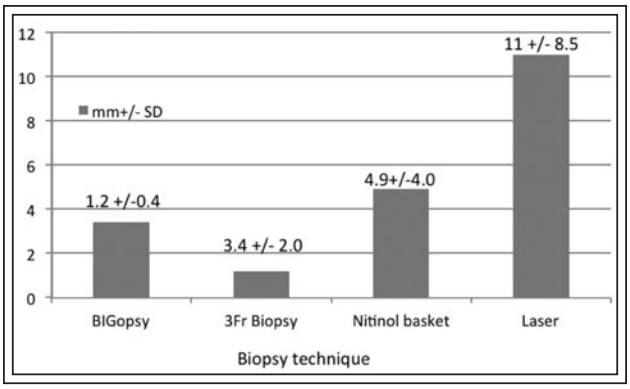

Figure 2. The mean size in maximal diameter (mm+/-SD) of the biopsies in each group.

cystica in one patient and papillary neoplasm in another patient. The other biopsies were either atypical and/or insufficient for pathologic diagnosis in the remaining four patients. The BIGopsy established a diagnosis of pTa high grade papillary urothelial carcinoma in one patient, pTa low grade papillary urothelial carcinoma in two patients, pTis in one patient, pyelitis cystica in one patient and benign urothelium in one patient (supplemental). Six patients went on to surgical extirpation with either a nephro or ureterectomy, three patients were managed endoscopically and one patient refused further treatment. Six patients had benign pathology. Final pathologic grading and staging data were available for six patients progressing onto surgical extirpation. In the three patients that were biopsied with the BIGopsy preoperatively, ureteroscopic grade and stage matched final surgical grade and stage in all 3/3 cases (pTis, pTa low grade and pT1 high grade).

One patient had extravasation on retrograde pyelogram following BIGopsy biopsy requiring ureteral stent placement for 3 weeks. Follow up CT urogram demonstrated no collecting system abnormalities. No other ureteroscopic complications were noted peri or postoperatively.

Discussion

We performed ex vivo and in vivo biopsies of urothelial tissue to directly compare standard 3Fr cold cup biopsy specimens to those obtained using a novel backloading biopsy forceps in patients with suspected UUC. In our ex vivo model using extirpated nephroureterectomy specimens we found that biopsies obtained with the BIGopsy were larger, less fragmented and subjectively were easier to interpret by the examining pathologist. In all three cases, the diagnosis based upon BIGopsy biopsy agreed with the final pathologic report, one of which was pathologically misassigned as malignant by the smaller 3Fr biopsy forceps. Smooth muscle was found in 1 of the 3 BIGopsy specimens and in none of the 3Fr biopsy forcep specimens. Our ex vivo model was limited by several factors including small sample sizes, unblinded data and was performed in a bloodless field taken by hand. Since our biopsy technique did not replicate true endoscopic conditions and the method used to obtain the biopsy could have easily affected the data, limited conclusions can be drawn from this aspect of our study. Recognizing these limitations we sought to further evaluate the efficacy of the BIGopsy ureteroscopic biopsy forceps in vivo and compare it to conventional biopsy tools.

We retrospectively reviewed our recent ureteroscopic experience in a similar cohort of patients with UUC. We found that for tumors on stalks, the basket snaring technique and/or en bloc laser excision allows for excellent tissue retrieval as compared to those obtained from biopsy forceps. Using a nitinol basket and/or endoscopic snare placed around the base of the tumor is a technique that has been described in the literature but is limited to case reports and small case series. Roome et al first described biopsy of intraureteral tumors by endoscopic means using either a standard cystoscopic biopsy forceps or a Johnson stone basket.[20] Others have described the use of stone baskets with or without the use of a ureteroscope and/or electrocautery.[13,21-25] Intuitively, snaring of a papillary tumor at the base allows near complete removal of the lesion while maintaining architecture for pathologic examination.

The first instruments for ablation and coagulation were 2 or 3F electrodes.[26] Laser energy has largely supplanted these earlier electrosurgical instruments and is used frequently to resect or ablate UUC in patients opting for endoscopic management.[22,26-30] Both the holmium: YAG and neodymium: YAG lasers can be delivered through small flexible fibers to reach all areas of the collecting system. The one theoretical advantage of laser energy over basket snaring is the ability to obtain deep biopsies so that lamina propria can be sampled. Caution must be exercised however when using laser energy around delicate areas of the collecting system (i.e. UPJ or ureter). To our knowledge, no randomized studies have been performed directly comparing these two modalities, largely due to the relative rarity with which these lesions are encountered. Although no significant conclusions can be drawn from our data due to small sample sizes, for tumors on stalks, basket snaring and/or laser excision appears to result in large specimens that maintains architecture and should be considered as the initial diagnostic modality.

For sessile and flat mucosal lesions the BIGopsy biopsy specimens were larger than those obtained with the 3Fr biopsy forceps, although this did not reach statistical significance. We found that the BIGopsy biopsy specimens were deeper than those obtained with the 3Fr biopsy forceps as suggested by the percentage of biopsies with lamina propria identified. Lamina propria was found in 23% of pathologic specimens biopsied with the 3Fr biopsy forceps as compared to 55% of the BIGopsy biopsy forceps. It is suggested that that the accuracy of preoperative staging can be improved with larger and deeper ureteroscopic biopsies. In our series, we found that this directly translated to improved diagnostic accuracy of biopsy specimens using the BIGopsy biopsy forceps. In the six patients biopsied using both biopsy forceps, the BIGopsy was able to make an accurate diagnosis in all six patients, whereas the 3Fr biopsy forceps was only able to establish a definitive diagnosis in two patients. This led to improved ability to counsel patients preoperatively and potentially altered management in 3/6 cases. Since lamina propria invasion is a surrogate for tumor aggressiveness one may consider surgical extirpation over endoscopic management in select patients.

In our series, final pathologic grading and staging data were available for six patients progressing onto surgical extirpation. Of the three that were biopsied with the BIGopsy, biopsy preoperatively, grade and stage matched final surgical grade and stage in all cases.

Although we recognize that our sample sizes are small and are limited to retrospective data that were not randomized, both our ex vivo and in vivo studies are consistent in demonstrating the ability of the BIGopsy to provide larger, deeper and less fragmented urothelial tissue to the examining pathologist. We found that this translates into improved ability to diagnose both benign and malignant lesions endoscopically which may potentially alter management.

Improved biopsy size and depth is a direct reflection of the larger biopsy head volume of the BIGopsy. The unique backloading design of the BIGopsy overcomes the challenges of working through the narrow and fixed working channel of the ureteroscope. In our experience we found that the trade off of a larger biopsy head is visualization. Having the biopsy head projecting from the ureteroscope requires careful navigation of the unit to prevent iatrogenic injury to unintended urothelium. Other limitations of the BIGopsy that we encountered are the need for a ureteral access sheath and greater flexion impairment than with standard 3Fr biopsy forceps. Despite these limitations we found that the majority of our upper tract lesions were able to successfully biopsied with minimal morbidity. The overall complication rate for our series was (5%), which increased to (11%) when we considered only those lesions biopsied with the BIGopsy. The one complication in our series included perforation of the renal pelvis following biopsy with the BIGopsy. This was recognized intraoperatively and confirmed by retrograde pyelogram. We were able to manage this conservatively with internal stenting and follow up demonstrated no long term sequelae. Although it was not an issue in our patient, there are potential consequences of collecting system perforation. Firstly, damage to the urothelium and underlying stroma could cause tissue contraction and scar formation; therefore one must use caution when biopsying tumors in the ureter, caliceal infundibula or other narrow regions of the collecting system. Secondly, there is a theoretical risk of tumor seeding. This is potentially a devastating complication that could ultimately affect cancer control and outcome. The urologist must therefore be vigilant in recognizing these complications intraoperatively.

Conclusions

Recognizing that this is a single institution experience with a novel ureteroscopic device, we found that baskets and/or laser excision provides the best specimen in appropriate cases with a stalk. For flat or sessile lesions, the BIGopsy biopsy forceps provided larger, deeper and less distorted specimens that were easier for the examining pathologist to interpret and correlated well with ultimate grade and stage. We hope that our findings will be confirmed by further prospective, randomized multi-institutional clinical studies with larger sample sizes. In the meantime, the BIGopsy appears to improve pathologic diagnosis and directed treatment in select upper tract lesions and is a welcome addition to our endourologic armamentarium. □

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