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Multi-institutional Evaluation of Upper Urinary Tract Biopsy Using Backloaded Cup Biopsy Forceps, a Nitinol Basket, and Standard Cup Biopsy Forceps

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Abstract

OBJECTIVE—To compare the performance of 3 contemporary ureteroscopic biopsy devices for the histopatho-logic diagnosis of upper tract urothelial carcinoma (UTUC).

METHODS—We retrospectively reviewed 145 patients who underwent 182 urothelial biopsies using 2.4F backloaded cup biopsy forceps, a nitinol basket, or 3F standard cup biopsy forceps at 3 tertiary academic centers between 2011 and 2016. Experienced genitourinary pathologists provided an assessment of each specimen without knowledge of the device used for biopsy. For patients who underwent nephroureterectomy without neoadjuvant chemotherapy within 3 months of biopsy- proven UTUC diagnosis, the biopsy grade was compared with both the grade and stage of the surgical specimen.

RESULTS—Biopsy utilization varied among the 3 institutions ($P < .0001$). Significant variabilities in speci- men size ($P = .001$), the presence of intact urothelium ($P = .008$), and crush artifact ($P = .028$) were found among the biopsy devices. The quality of specimens from backloaded cup forceps was rated similarly to the nitinol basket ($P > .05$) and was favored over standard cup forceps speci- mens. Grade concordance was not affected by specimen size ($P > .05$), morphology ($P > .1$), or lo- cation ($P > .5$). No difference existed among the devices in the rate of acquiring a grade concordant biopsy; however, the backloaded cup forceps provided concordant biopsies that could be distin- guished as low- and high-grade ($P = .02$).

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CONCLUSION—The backloaded cup forceps and nitinol basket obtained a higher quality urothelial specimen compared with standard cup forceps. Ureteroscopic biopsy device selection did not significantly impact the accuracy of the histologic diagnosis of UTUC. UROLOGY 117: 89–94, 2018.

Keywords

biopsy forceps; nitinol basket; upper tract urothelial carcinoma; urothelial biopsy

Upper tract urothelial carcinoma (UTUC) repre-sents 5% of urothelial malignancies with approxi-mately 3600 new cases resulting in 900 deaths in 2017.[1] Accurate histopathologic diagnosis is crucial, as multifocality, tumor grade, and tumor stage are key prog-nostic determinants.[2,3]

The biopsy needed for the diagnosis of UTUC is typi-cally obtained using an endoscopic retrograde approach.[4,5] Most modern flexible ureteroscopes have a 3.6F working channel, which limits the size of the biopsy device that can be utilized. Small biopsy size results in insufficient and frag-mented specimens that are often inadequate for an accu-rate histopathologic diagnosis.[6] Indeed, the literature has shown the potential to underdiagnose UTUC when using contemporary ureteroscopic biopsy devices.[7,8] Collec-tively, these findings highlight the importance of obtaining a sufficient, high-quality specimen during upper urinary tract biopsy.

Specimen size and preservation of histologic architecture serve an important role in making an accurate diag-nosis of UTUC.[9,10] In an effort to solve the limitations of small caliber biopsy devices, the backloaded cup biopsy forceps was developed. The modified tissue cup design of the backloaded cup forceps has been shown to provide deeper and larger tumor specimens.[6,11] To assess perfor-mance of the backloaded cup forceps among contempo-rary ureteroscopic biopsy devices, we performed a multicenter, retrospective evaluation of the quality and ac-curacy of urothelial biopsies that were acquired using the backloaded cup biopsy forceps, a nitinol basket, or a stan-dard cup biopsy forceps.

METHODS

A retrospective review of all endoscopic upper urinary tract biopsies at 3 tertiary centers between January 2011 and August 2016 was performed with institutional review board approval. We included patients ≥18 years old who under-went urothelial biopsy using either the 2.4F backloaded cup biopsy forceps (BIGopsy backloading biopsy forceps, Cook Medical Inc., Bloomington, IN), a nitinol basket (2.4F NCircle, Cook Medical Inc., Bloomington, IN), or 3F stan-dard cup biopsy forceps (Piranha forceps, Boston Scien-tific Corp., Newport Beach, CA). Biopsies obtained with more than 1 of the aforementioned devices or alternative methods were excluded. Patient demographics, Charlson Comorbidity Index, and risk factors for urothelial carci-noma were recorded. The Department of Urology at the University of California, Irvine coordinated the transfer and storage of de-identified data included in the study.

The technique for upper urinary tract biopsy varied by institution. In general, urothelial biopsies were obtained in a retrograde fashion; specimens from the renal pelvis were acquired utilizing flexible ureteroscopy, and ureteral biop-sies were acquired using a semirigid ureteroscope. In select cases, multiple specimens were acquired during a single pro-cedure. Importantly, a ureteral access sheath (UAS) was deployed prior to use of the backloaded cup forceps.

Urothelial biopsies were transported in physiologic saline and fixed and stained with hematoxylin and eosin prior to review. A rereview of each urothelial specimen was per-formed to obtain biopsy location, size and quantity of speci-mens per biopsy, specimen morphology as described in the biopsy operative report, rate of definitive diagnosis, crush artifact, intact urothelium, lamina propria, muscularis propria, and World Health Organization grade classifica-tion by experienced genitourinary (GU) pathologists with no knowledge of the biopsy device. Subsequently, a single GU pathologist from each institution (T.K.L., J.P.B., and T.M.S.), also unaware of the biopsy device used, com-pleted a Likert-type questionnaire (ie, 1 = poor or low confidence to 10 = excellent or high confidence) to subjectively evaluate each biopsy specimen (Supplementary Table A).

The final pathology for patients who underwent nephroureterectomy (NU) within 3 months of biopsy-proven UTUC was recorded to compare the biopsy speci-men with the NU specimen to assess for grade concordance. Furthermore, the relationship between the biopsy grade (ie, low- or high-grade) and final pathologic stage (ie, low-stage [pTa-T1] or high-stage [pT2-T4])[12] was noted for pa-tients who did not undergo neoadjuvant chemotherapy nor previous ureterectomy or laser ablation.

Continuous variables were analyzed using independent paired samples *t* test or Mann Whitney *U* test. Categori-cal variables were analyzed using chi-square test and Fish-er's exact test where appropriate. All reported *P*-values are 2-sided. Multivariate logistic regression was used to examine the concordance between the biopsy and NU specimen grade with adjustment for biopsy location. Secondary out-comes included the rate of the biopsy specimen being di-agnostic and the presence of crush artifact. A multivariate mixed linear model was used to compare the pathologist questionnaire with adjustment for biopsy location. Odds ratio calculations specifically took into account the loca-tion of the biopsy. Statistical analysis was performed with SPSS version 21 (SAS Institute Inc., Cary, NC) with a $P < .05$ considered as significant.

RESULTS

One hundred and forty-five patients underwent 182 urothelial biopsies: 71 specimens (39%) were obtained using backloaded cup forceps, 72 specimens (40%) using the nitinol basket, and 39 specimens (21%) using standard cup forceps. Twenty-one urothelial samples (11%) were re-ported as benign and 137 samples (75%) as malignant; no difference was found in the rate of definitive diagnosis among the devices ($P = .281$). Biopsy device utilization varied significantly among the institutions (Fig. 1); however, baseline patient characteristics were similar among the biopsy devices (Table 1).

Compared with the standard cup forceps, the backloaded cup forceps and the nitinol basket obtained significantly larger specimens (4.1 ± 3 mm and 4.3 ± 2.3 mm vs 2.4 ± 1.9 mm, respectively, $P < .001$) with intact urothelium (73% and 65% vs 44%, respectively, $P < .05$) (Table 1). The frequency of specimens free of crush artifact was signifi-cantly greater using the nitinol basket compared with stan-dard cup forceps (14% vs 36%, respectively, $P = .014$).

UTUC was diagnosed for 96 papillary lesions (87%) and 26 sessile lesions (70%). The backloaded cup forceps was utilized more frequently for sessile lesion biopsies than the nitinol basket ($P = .07$); however, the amount of papil-lary specimens acquired using the nitinol basket was sig-nificant ($P = .024$). Compared with standard cup forceps, the backloaded cup forceps obtained larger sessile lesion biopsies (4.0 ± 1.6 mm vs 3.0 ± 2.4 mm, respectively, $P = .071$) and papillary lesions biopsies (4.8 ± 2.3 mm vs 2.3 ± 1.9 mm, respectively, $P < .01$). Papillary specimen size using backloaded cup forceps and nitinol basket papillary were similar (4.8 ± 2.3 mm vs 4.5 ± 3.0 mm, respectively, $P > .5$). A significant amount of papillary lesion biopsies with lamina propria present were acquired by the backloaded cup forceps compared with the nitinol basket (92% vs 69%, $P = .024$) or standard cup forceps (92% vs 64%, $P = .022$). Furthermore, the rate of papillary lesion biopsies with intact urothelium using backloaded cup forceps was signifi-cantly greater than standard cup forceps (86% vs 55%, $P = .018$). Biopsy performance for sessile lesions did not differ among the devices ($P > .5$).

Of the 96 patients who underwent NU, 74 surgical speci-mens (77%) were concordant with the urothelial biopsy grade (Table 2A). There was no difference in the fre-quency of a grade concordant biopsy among the devices (Table 1); however, the ability to distinguish low- or high-grade UTUC prior to NU was significant using the backloaded cup forceps ($P = .02$) and approached signifi-cance using the nitinol basket ($P = .05$) (Table 2A). After stratifying 91 NU specimens based on biopsy morphology (Table 2B), there were no differences in grade concor-dance based on endoscopic growth pattern. No relation-ship between specimen size and concordance was detected ($P = .815$). In addition, biopsy location (ie, ureter or renal pelvis) did not affect concordance (odds ratio 1.29, $P = .603$; 95% confidence interval: 0.5–3.35).

The final pathology for 81 NU specimens was com-pared with the corresponding urothelial biopsy. Agree-ment between the biopsy grade and NU stage occurred in 47 patients (58%); the subset of patients whose biopsy was conducted utilizing backloaded cup forceps was predic-tive of the extent of disease following NU (Table 2C).

The backloaded cup forceps received a significantly greater subjective score for biopsy quality ($P = .012$), quality of basement membrane thickness ($P = .021$), and role of biopsy size in accurate diagnosis ($P = .043$) compared with standard cup forceps (Table 3). No subjective differences were found between the backloaded cup forceps and nitinol basket biopsies. Lastly, irrespective of the biopsy device uti-lized, ureteral biopsies were rated superior in quality com-pared with specimens from the renal pelvis ($P = .025$).

DISCUSSION

Endoscopic biopsy for UTUC has proven to be an ongoing challenge for urologists. Although NU remains the gold standard for definitive treatment,[2] highly selected UTUC can be managed endoscopically. Nephron-sparing ureteroscopic treatment can benefit patients with a soli-tary functioning kidney, high-grade chronic kidney disease, or those with severe comorbidities.[13,14] The management of these patients varies widely, and the decision-making process is heavily influenced by the urothelial biopsy.[15–18] Often, patients with low-grade, low-stage disease can be managed ureteroscopically,[19–22] whereas high-grade, inva-sive UTUC commonly requires a more aggressive renal ab-lative approach.[2,23] Our multicenter study sought to determine the accuracy of endoscopic management utiliz-ing 3 different contemporary biopsy devices for the initial diagnosis of UTUC before divergence of the treatment plan proceeded.

In the present study, we found that 77% of urothelial biopsies provided an accurate clinical diagnosis of UTUC. Previously, estimate of urothelial biopsy accuracy using con-temporary devices was reported as high as 75%, yet indi-vidual device concordance is not routinely reported.[24,25] Keeley et al[26] studied 51 cases of UTUC treated with NU, a number of which were biopsied with a nitinol basket or cup forceps, and reported 90% of low- and high-grade bi-opsies were concordant with the NU specimen, whereas 86% of low-grade and 67% of high grade biopsies corre-sponded to low- and advanced-stage disease, respectively. Keeley et al[26] also found a near doubling in the rate of graded urothelial specimens using cell block preparation (43%−97%) compared with whole biopsy tissue histopathology, which was used in the present study. In another series, Smith et al[7] found that UTUC severity was underestimated after the initial endoscopic biopsy in patients who underwent repeat biopsy or NU, with reclassification to high-grade or invasive disease occurring in 43% of patients upon final histopathologic diagnosis. The authors suggested that the discrepancies were related to inaccuracy of the initial biopsy and insufficient tissue sampling without mention of the spe-cific biopsy device(s) used. However, Rojas et al[27] evalu-ated the impact of specimen size in concordant urothelial biopsies obtained with standard cup forceps or a Segura basket and reported a high rate of concordance that was independent of specimen volume. In addition, they con-cluded that the presence of suburothelial tissue tended to result in disagreement between the biopsy and surgical speci-men, yet the significance of this finding was unclear con-sidering a majority of the study cohort had high-grade disease.

The discrepancies in specimen quality may be attributable to differences in device design. Indeed, the standard cup forceps has 25% of the tissue collecting capability of the backloaded cup forceps (1 mm^3 vs 4 mm^3, respec-tively), and both lack the nitinol basket's ability to ensnare a specimen from its base. The backloaded cup forceps cap-tures a large specimen, yet its substantial cup volume can reduce the endoscopic field of view by 20% and necessi-tates the added cost and placement of a UAS or the use of a double lumen ureteroscope to mitigate the change in working channel flow.[6,11,28] In contrast, the nitinol basket can be front loaded with negligible effect on flow and vi-sualization. To further investigate the clinical impact of ureteroscopic biopsy design, Al-Qahtani et al[11] prospec-tively collected urothelial biopsies after randomizing speci-men collection to either backloaded or standard cup forceps. A pathologist blinded to the biopsy device used found

that 80%−85% of specimens to be larger and provided suffi-cient tissue for definitive diagnosis compared with 45% using standard cup forceps. Moreover, Wason et al[6] evaluated several ureteroscopic biopsy devices and found that stalked lesions were sampled best using a laser to cut the speci-men combined with a nitinol basket retrieval; however, when sampling sessile lesions, the backloaded cup forceps collected larger specimens that were superior in quality and grade concordance compared with standard cup forceps. Kleinmann et al[29] found superior performance with use of a flatwire basket compared with standard cup forceps and suggested that the basket's larger intact specimens may be the source of a greater rate of pathologic diagnosis.

We identified differences in histologic quality and pa-thologist preferences for urothelial biopsy; however, after reviewing the raw data carefully, given the nearly identi-cal concordance rates, the authors feel that a concrete con-clusion cannot be drawn regarding the superiority of the backloaded cup forceps over the nitinol basket despite our significant findings. It is possible that a powered study may better differentiate the relationship between ureteroscopic biopsy device and acquiring a grade concordant urothelial specimen that also is predictive of the extent of disease. Given our findings, optimal urothelial biopsy is likely achieved on a case-by-case basis, noting the location, mor-phology, and size of the biopsy to be obtained. Jeon et al[30] found that invasion of the lamina propria was present in 84% of patients with >pT2 stage UTUC, albeit with the standard cup forceps obtaining lamina propria in half of its specimens, which is similar to our findings (Table 1). Thus, the presence of lamina propria cannot be under-stated and reinforces routine ureteroscopic evaluation for UTUC and may improve the selection of patients for neoadjuvant chemotherapy if pursuing NU. Thus, our results support previous reports that highlight the diffi-culty in identifying a ureteroscopic biopsy device with su-perior function based on quality and size of the urothelial specimen.

There are limitations to our multi-institutional study in addition to its retrospective design. We recognize that there are other instrumentation and methods for urothelial biopsy aside from the ureteroscopic devices we reviewed. Further-more, device utilization varied significantly among the in-stitutions and the inherent differences in biopsy technique, including the specific ureteroscope and frequency of UAS use for all biopsy devices, may be the reason our results lack measureable differences between diagnostic accuracy. It is possible that surgeons select the most appropriate tool to sample urothelium based on specific lesion attributes. In this regard, a survey of the urothelial biopsy method pre-ferred by experienced endourologists and urologic oncolo-gists would provide valuable insight into situations in which a specific biopsy device is indicated. Although there were subjective differences in the quality of the urothelial speci-mens among the 3 devices, the clinical relevance of our results would be stronger having had all 3 GU patholo-gists review all samples included. Ultimately, a prospec-tive, randomized design would be of great value, as it would eliminate selection bias and incorporate a standardized re-porting protocol for all variables studied. Lastly, although the backloaded cup forceps commonly requires use of a UAS, we make use of a dual working channel flexible ureteroscope (Cobra, Richard Wolf Endoscopy, Vernon Hills, IL) at our institution, which has enhanced flow properties that may mitigate the disturbance in flow when using the backloaded cup forceps with a single channel ureteroscope.

CONCLUSION

The quality of urothelial biopsy was improved using the backloaded cup forceps and a nitinol basket compared with standard cup forceps. Our results suggest that utilization of a ureteroscopic device for biopsy of urothelial lesions sus-picious for UTUC is often appropriately selected by ex-perienced endourologists and urologic oncologists, and thus a single ureteroscopic biopsy device that is superior for urothelial biopsy is not easily distinguishable.

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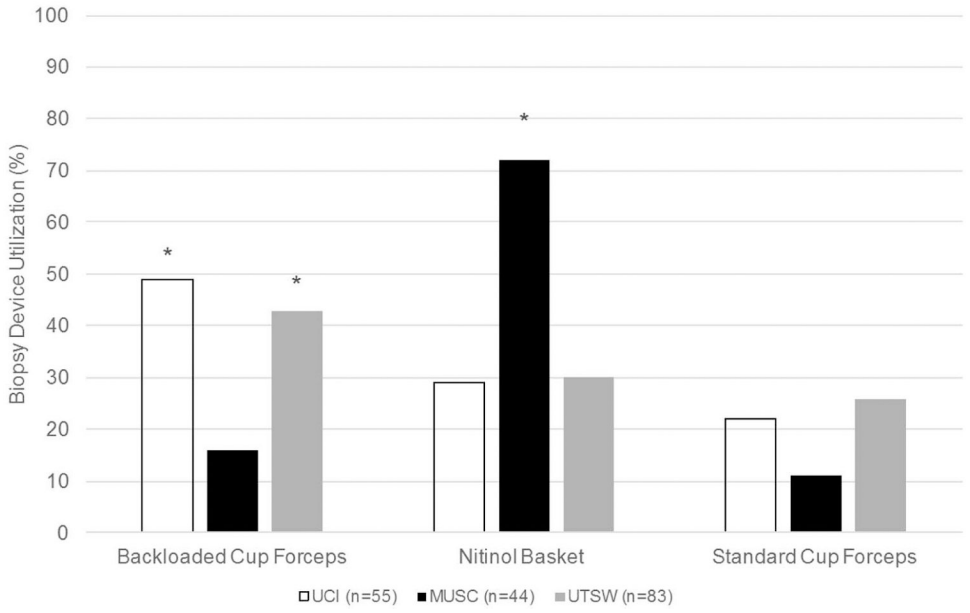

Figure 1.
Frequency of biopsy device utilization per institution (*P <.0001).

Table 1.

Patient and urothelial biopsy characteristics for each ureteroscopic biopsy device.

Variable	Backloaded Cup Forceps (n = 71)	Nitinol Basket (n = 72)	Standard Cup Forceps (n = 39)	*P*
Age (mean ± SD)	69 ± 10.4	70.3 ± 13	71.5 ± 10.3	.611
Male (%)	22 (31)	30 (41)	13 (33)	.251
BMI (mean ± SD)	28.3 ± 6	27.2 ± 5.4	27.2 ± 3.4	.48
CCI (mean ± SD)	4.4 ± 2.4	5.1 ± 2.4	4.7 ± 1.9	.278
Smoking (%)	39 (55)	41 (57)	15 (38)	.175
Alcohol (%)	21 (29)	14 (19)	8 (20)	.413
Diabetes mellitus (%)	13 (18)	6 (8)	18 (46)	.399
Number of samples per biopsy (mean ± SD)	2.6 ± 1.7	2.4 ± 1.7	2.6 ± 1.5	.291
Biopsy size, mm (mean ± SD)	4.1 ± 3	4.3 ± 2.3	2.4 ± 1.9	.001
Papillary lesion (%)	36 (51)	52 (72)	22 (56)	.048
Sessile lesion (%)	18 (25)	9 (12)	10 (25)	.248
Biopsies lacking growth pattern description (%)	17 (24)	11 (15)	7 (18)	–
Definitive diagnosis made * (%)	64 (90)	63 (87)	31 (79)	.281
Presence of intact urothelium (%)	52 (73)	47 (65)	17 (44)	.008
Presence of lamina propria (%)	61 (86)	51 (71)	27 (69)	.052
Presence of muscularis propria (%)	4 (5)	2 (3)	0 (0)	.292
Presence of crush artifact (%)	17 (24)	10 (14)	14 (36)	.028
Malignant biopsy (%)	55 (77)	58 (81)	24 (62)	.073
Low-grade UTUC biopsy (%)	26 (37)	33 (46)	12 (31)	.395
High-grade UTUC biopsy (%)	29 (41)	25 (35)	12 (31)	
Grade concordance (%)	55 (78)	56 (78)	29 (75)	.177
Low-stage surgical specimen (≤pT1) (%)	21 (29)	16 (22)	8 (20)	.855
High-stage surgical specimen (≥pT2) (%)	15 (21)	13 (18)	8 (20)	

BMI, body mass index; CCI, Charlson Comorbidity Index; SD, standard deviation, UTUC, upper tract urothelial carcinoma.

* Definitive diagnosis refers to urothelial specimens that were deemed benign or malignant UTUC and excludes specimens that were indeterminate per pathologist review.

Table 2.

A, presence or absence of concordance for patients with low- or high-grade biopsy specimens who underwent nephroureterectomy. B, presence or absence of concordance for papillary and sessile lesions. C, correspondence between biopsy grade and surgical stage for each biopsy device

A.	Backloaded Cup Forceps			Nitinol Basket			Standard Cup Forceps		
Grade of Biopsy Specimen	**Low-grade (n = 17)**	**High-grade (n = 23)**	***P***	**Low-grade (n = 18)**	**High-grade (n = 22)**	***P***	**Low-grade (n = 10)**	**High-grade (n = 6)**	***P***
Concordant (%)	10 (59)	21 (91)	.02	11 (61)	20 (91)	.05	7 (70)	5 (83)	1.00
Not concordant (%)	7 (41)	2 (9)		7 (39)	2 (9)		3 (30)	1 (17)	
B.									
Endoscopic Appearance	**Papillary (n = 24)**	**Sessile (n = 11)**	***P***	**Papillary (n = 34)**	**Sessile (n = 5)**	***P***	**Papillary (n = 12)**	**Sessile (n = 5)**	***P***
Concordant (%)	19 (79)	9 (82)	1.00	27 (79)	4 (80)	1.00	9 (75)	2 (40)	.28
Not concordant (%)	5 (21)	2 (18)		7 (21)	1 (20)		3 (25)	3 (60)	
C.									
Surgical Stage	**Low-grade Biopsy (n = 12)**	**High-grade Biopsy (n = 24)**	***P***	**Low-grade Biopsy (n = 8)**	**High-grade Biopsy (n = 21)**	***P***	**Low-grade Biopsy (n = 3)**	**High-grade Biopsy (n = 13)**	***P***
Low-stage specimen, pTa-pT1 (%)	10 (83)	11 (46)	.04	6 (75)	10 (48)	.24	1 (33)	7 (54)	1.00
High-stage specimen, pT2-pT4 (%)	2 (17)	13 (54)		2 (25)	11 (52)		2 (67)	6 (46)	

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Table 3.

Mixed linear regression of pathologist questionnaire scores for biopsy device specimen

Criteria	Score Difference (Mean ± SE)				
	Backloaded Cup Forceps	**Nitinol Basket**	***P***	**Standard Cup Forceps**	***P***
Biopsy quality	Referent	0.83 ± 0.5	.109	−1.38 ± 0.51	.012
Confidence in final diagnosis	Referent	0.63 ± 0.38	.115	−0.59 ± 0.41	.158
Ease of interpretation	Referent	0.82 ± 0.40	.054	−0.60 ± 0.41	.161
Quality of basement membrane thickness	Referent	0.32 ± 0.62	.606	−1.52 ± 0.61	.021
Role of biopsy size in accurate diagnosis	Referent	−0.20 ± 0.39	.613	−0.82 ± 0.38	.043

SE, standard error.