World Journal of Urology (2019) 37:1899–1905
https://doi.org/10.1007/s00345-018-2586-y

ORIGINAL ARTICLE

Comparison of biopsy devices in upper tract urothelial carcinoma

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Received: 14 August 2018 / Accepted: 27 November 2018 / Published online: 17 December 2018

Abstract

Introduction A correct characterization of upper tract urothelial carcinoma (UTUC) lesions is fundamental to appropriately select patients suitable for endoscopic management. We analyzed the diagnostic yield of three different biopsy tools for the histology evaluation of the UTUC. Furthermore, the concordance between biopsy grading and final UTUC pathology results at specimen (i.e., after ureterectomy or radical nephroureterectomy—RNU) was evaluated.

Materials and methods Three different devices were evaluated: 3F biopsy forceps, 6F BIGopsy® Backloading biopsy forceps and the 2.2F Nitinol Basket. Data were collected between January 2015 and October 2017 and retrospectively analyzed. Univariate and multivariate logistic regression analyses were performed to identify the variables related to diagnosis.

Results A total of 302 biopsies were taken: lesions could be characterized in 236 (78.2%) specimens by the pathologist. Positive biopsies for UTUC were found in 140 specimens. In 66 biopsies (21.8%), the quality of the tissue sampled was inadequate for a histological characterization; of these, 55 (83.3%) were taken using 3F forceps and 11 (16.7%) using BIGopsy forceps. No inadequate specimen arose using the 2.2F Nitinol Basket. Among 28 patients who underwent distal ureterectomy or RNU, the tumor was upgraded to high grade in 9 (32%), while in 19 (68%) the grading was confirmed.

Conclusion In comparison to 3F forceps, the BIGopsy forceps showed to be more accurate in obtaining sufficient specimen for pathologic examination. In papillary lesions, the 2.2F Nitinol basket achieves a final histology characterization in 100% of the cases. For tumor < 2 cm, there is a high concordance between URS biopsy grade and final pathology (distal ureterectomy or RNU).

Keywords Biopsy · Flexible ureteroscopy · Nephro-sparing surgery · Upper tract urothelial carcinoma

Abbreviations

CIS	Carcinoma in situ
CT	Computed tomography
EAU	European Urology Association
f-URS	Flexible ureteroscopy
sr-URS	Semirigid ureteroscopy
NSS	Nephro-sparing surgery
RNU	Radical nephroureterectomy
URS	Ureteroscopy
UTUC	Upper tract urothelial carcinoma

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Introduction and aims of the study

Upper tract urothelial carcinoma (UTUC) accounts for only 5% of all transitional cell carcinomas and less than 10% of renal tumors [1–3]. Radical nephroureterectomy (RNU) with ipsilateral bladder cuff excision is the gold standard treatment for UTUC [3–5]. Despite the oncologic efficacy of this radical approach, it is associated with high morbidity and loss of nephron units. According to the European Urology Association (EAU) guidelines on UTUC, nephro-sparing surgery (NSS) is recommended in imperative cases, such as an anatomic or functional solitary kidney, bilateral tumors, or poor baseline renal function [1]. However, NSS may be extended to patients with non-imperative indications (elective cases), and many series have highlighted excellent oncologic and functional outcomes in patients with unifocal, small (< 2 cm), low-grade and non-muscle-invasive UTUC [1].

CT urography has become the new gold standard for tumor detection. It allows detection of the UTUC lesion by identifying filling defects, contrast enhancing mass lesions, wall thickening, or hydroureteronephrosis for undetermined causes. The sensitivity, specificity, and accuracy of CT urography for the detection of UTUC have been reported to be 93.5–95.8%, 94.8–100%, and 94.2–99.6%, respectively [6]. Furthermore, urine cytology is less sensitive for UTUC than for bladder cancer, even in the case of high-grade tumors [7].

In both elective and imperative cases, UTUC grading and staging are mandatory to establish the best treatment (conservative vs. radical) [8, 9]. The current endourological tools allow for the visualization of the lesions as well as their sampling, improving the overall diagnostic accuracy [10]. Despite this, the consistent sampling of sufficient tissue for pathologic evaluation remains challenging and the ideal biopsy device is not yet available.

With this study, we have aimed to evaluate the different performance of three endoscopic devices in forceps allowing for histology characterization, to appropriately select patients suitable for endoscopic/conservative management.

Materials and methods

Study design, variables and outcomes

Between January 2015 and October 2017, a single-center prospective study was undertaken. Data on patients who underwent URS procedures for UTUC were retrospectively reviewed and analyzed. Three different devices were analyzed: 3F biopsy forceps (Karl Storz, Tuttlingen, GE), 6F BIGopsy® Backloading biopsy forceps (Cook Medical, Bloomington, IN), and the 2.2F Nitinol basket (Cook Medical, Bloomington, IN) (Fig. 1) to evaluate the diagnostic yield obtained by either forceps or the 2.2F Nitinol basket. According to our protocol, one biopsy per device (i.e., three per patient) was performed, when all devices were used. In case of only one device was used, a minimum of two biopsies were taken per patient. As second outcome, we evaluated the association between URS biopsy grading and final UTUC pathology results when distal ureterectomy or RNU was carried out.

Surgical procedure

Patients underwent semirigid URS (sr-URS) or flexible URS (f-URS) for newly diagnosed UTUC as well as for UTUC surveillance, performed by a dedicated team involved in UTUC conservative treatment. In all cases, endourological

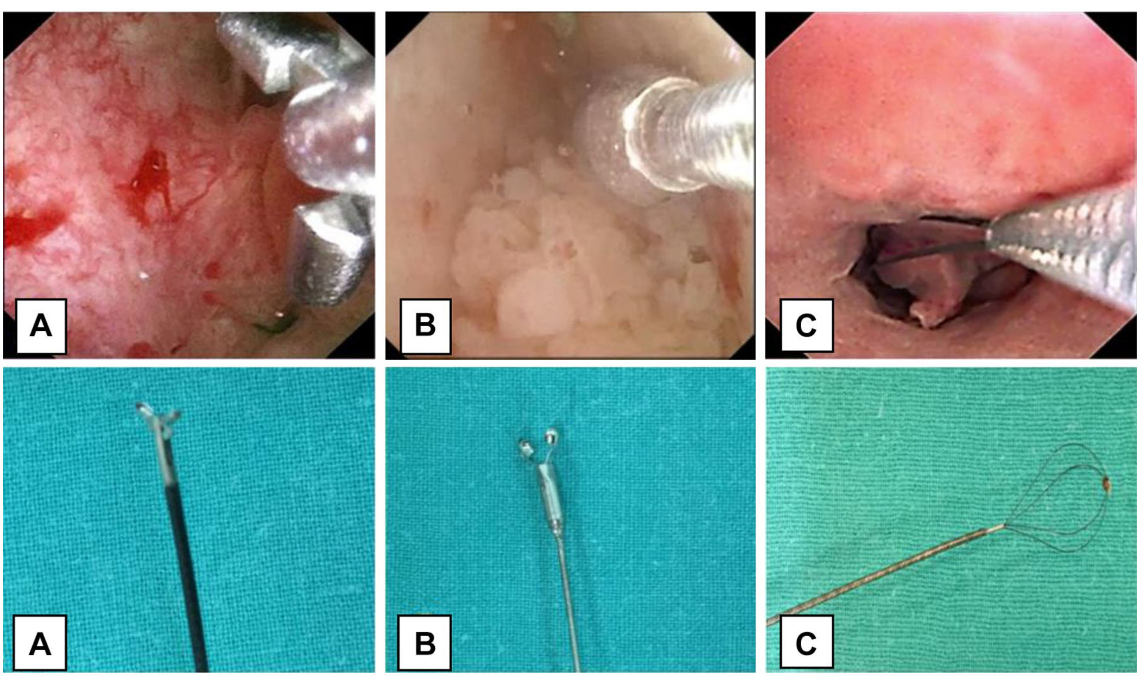

Fig. 1 **a** 3F biopsy forceps (K. Storz, Tuttlingen, GE). **b** 6F Bigopsy® Backloading biopsy forceps (Cook Medical, Bloomington, IN). **c** 2.2F Nitinol Basket (Cook Medical, Bloomington, IN)

evaluation also included IMAGE ST1 inspection (Flex X^C, Karl Storz) with particular emphasis in Clara + Chroma and Spectra B modalities to increase the accuracy of white light inspection. Following retrograde access, UTUC of the distal ureter was inspected with sr-URS, while the remainder of the ureter, the renal pelvis, and the calyces were checked with f-URS. This latter was preferably performed using a "non-touch technique" whereby the entire urinary tract was visualized before the insertion of guidewires to avoid trauma or bleeding that might affect the detection of the lesions. Sampling of the suspicious lesion was attempted with the three devices in observation forceps.

In more detail, when using the 2.2F Nitinol basket, the tumor was trapped within the wires and by gently pulling the basket a piece or even the whole tumor was removed. Due to the smaller caliber of the basket, sampling of lesions in the more difficult-to-reach calyces was more likely to be successful; on the other side, flat lesions could not be sampled with this tool. Instead, the BIGopsy forceps needed to be introduced in the f-URS by back loading through the working channel as the tip of the device is 6 F in caliber; because of the consequent lack of irrigation fluid, an ureteral access sheath was placed to allow the insertion of the f-URS with the BIGopsy. Another drawback of the device was the stiffness provided to the scopes, so that sampling of lesions (either flat or papillary) could be possible if no deflection was needed.

Urine samples were collected for cytology. UTUC lesions (< 2 cm) were treated using monopolar coagulation and/or holmium laser ablation. The setting of this latter consisted of a frequency range of 10–12 Hz with the energy ranging from 0.8 to 1.2 J. Tumor grading was assessed according to the 2004 World Health Organization classification system. The same dedicated UTUC pathologist examined all specimens. Tumor stage was determined using the TNM criteria according to CT findings.

Statistical analysis

The frequency and valid percentage of the qualitative variables were determined. Regarding the quantitative variables, measurements of central tendency were used, i.e., mean/median, measurements of position (quartiles), and dispersion [standard deviation or interquartile range (IQR)]. Clinical variables in relation to the biopsy device used were assessed by means of the Chi-square test (Fisher test for frequencies < 5) in the case of categorical variables as well as of the non-parametric ANOVA test in the case of quantitative variables. Multivariate analyses using a backward stepwise logistic regression model were performed to identify the variables related to diagnosis Cohen's Kappa was estimated to evaluate inter—rater agreement between the biopsy and the final histopathology result in grading assessment. For all the tests, a p value < 0.05 was considered significant. The statistical package SPSS (V 23) was used.

Results

Descriptive characteristics

Data on 85 patients who underwent URS procedures for UTUC were retrospectively reviewed and analyzed. Data extracted included patient demographic characteristics, tumor side (right, left, bilateral), and biopsy location (ureter, pelvis, calyx) (Table 1).

Surgical data and pathology results

A total of 112 diagnostic and therapeutic sr-URS and f-URS procedures were performed, and 302 biopsies were taken using the three biopsy devices (3F forceps, BIGopsy forceps, and 2.2F Nitinol basket—Fig. 1). Mean (SD) specimen size was 1.3 (SD 0.5), 3.2 (SD 1.4), and 4.3 (SD 1.9) mm using the 3F forceps, BIGopsy, and 2.2F Nitinol basket, respectively ($p < 0.001$).

Overall, a successful histology characterization was achieved in 236 (78.2%) of the 302 biopsies. Specifically, the 3F forceps achieved a diagnosis in 164/219 specimens (74.9%), compared with 50/61 (81.9%) in the BIGopsy forceps group and 22/22 (100%) in the 2.2F Nitinol basket group ($p = 0.001$) (Table 2). In 66/302 (21.8%) biopsies, the specimen was inadequate to establish an accurate diagnosis; of these, 55 (83.3%) were obtained using 3F forceps and 11 (16.7%) using BIGopsy forceps. Among those procedures in whom a histological characterization was achieved ($n = 236$), 140 (59%) biopsies positive for UTUC were found. Of these, 75 (53.6%) were low grade, 50 (35.7%) high grade, and 15 (10.7%) carcinoma in situ (CIS).

In a subgroup of 27 patients where both forceps 3F forceps and BIGopsy were used to sampling the same lesion, histological characterization resulted to be the same in 20 of them (74.1%), as follow: 14 low grade, 5 high grade, and 1 CIS. In the remaining seven cases (25.9%), the specimen obtained using the 3F forceps was inadequate to establish an accurate histology evaluation.

Staging could not be assessed in 129/140 (92.1%) of the specimen (Tx), while in 11/140 (7.9%) non-invasive papillary carcinoma was diagnosed (Ta) using the three biopsy devices. With respect to tumor staging, no device displayed superiority over the others.

Specimen size, forceps, location, tumor size, and visible lesions were included as independent variables in the logistic regression model to investigate their diagnostic significance. More in details, we categorized as visible those lesions

Table 1 Data on demographic characteristics, tumor side, and biopsy location

	n	%
Age (years)		
Mean (SD)	71.32 (9.28)	
Median (min–max)	71 (47–90)	
Sex ($n=85$)[a]		
Male	70	82.4
Female	15	17.6
Previous urothelial tumor ($n=85$)[a]		
No	35	42.2
Yes	43	50.6
Unknown	7	7.2
Ureteroscopy side ($n=112$)[b]		
Left	62	55.4
Right	44	39.2
Bilateral	6	5.4
Biopsy location ($n=302$)[c]		
Ureter	170	56.3
Pelvis	92	30.4
Calyx	40	13.3

[a]Number of patients

[b]Number of ureteroscopies

[c]Number of biopsies

macroscopically evident (papillary or sessile), while the non-visible lesions consisted in the suspicious “flat” areas.

Specimen size (OR = 1.95, $p=0.003$) and visible lesions (OR = 3.55, $p<0.001$) were found to be significantly related to a successful histological characterization in the univariate analysis, as were use of BIGopsy forceps in comparison with 3F forceps (OR = 4.25, $p=0.018$) and acquisition of the biopsy sample from the calyx in comparison with the ureter (OR = 5.17, $p=0.048$). The multivariate model showed that the only use of BIGopsy forceps (OR = 3.42, $p=0.049$) and visible lesions (OR = 2.63, $p=0.009$) was independently related to diagnosis (Table 3). Grade and specimen size were not included since valid values were not registered for all categories. The 2.2F Nitinol Basket was not included in the univariate and multivariate analysis due to the low number of the biopsies collected using it, compared to the others biopsy devices.

Another aim was to evaluate the association between URS biopsy grading and final UTUC pathology results when distal ureterectomy ($n=9$) or RNU ($n=19$) was carried out. Among the 28 patients who underwent distal ureterectomy or RNU, 9 (32%) were upgraded on final pathology, while in 19 (68%) of these the tumor grading was confirmed; regarding the 9 cases upgraded at final pathology, 9/9 were tumors > 20 mm in size (mean: 36.3 mm). Particularly, Cohen’s Kappa was 0.50 (moderate grade of agreement). One case of pelvic squamous cell carcinoma was found (not included among the UTUC cases) and RNU was performed.

According to the Satava classification [12], there were no biopsy-related intra-operative complications. One case of post-operative bleeding was recorded and it was managed conservatively (grade 1, according to Clavien–Dindo classification) [13].

Discussion

The management of UTUC has changed radically over the last two decades thanks to technological advances and better understanding of its biologic behavior. Nephro-sparing surgery allows avoidance of the great morbidity of RNU while maintaining oncologic outcomes [14]. UTUC may be treated conservatively using an endourologic approach (retrograde and/or anterograde URS, percutaneous approach) or segmental ureterectomy [1, 15].

Table 2 Biopsy characteristics

	3F forceps ($n=219$)	6F forceps (BIGopsy) ($n=61$)	2.2F nitinol basket ($n=22$)	Total	*p*
Biopsy size (mm) ± SD	1.3 ± 0.5	3.2 ± 1.4	4.3 ± 1.9	–	< 0.0001
Papillary/sessile lesion	68 (59.0%)	25 (21.7%)	22 (19.3%)	115	< 0.0001
Flat lesion	151 (80.7%)	36 (19.3%)	0 (0%)	187	< 0.0001
Histological characterization	164 (69.5%)	50 (21.2%)	22 (100%)	236	0.028
Benign lesion	80 (83.3%)	13 (13.5%)	3 (3.2%)	96	0.0003
Malignant lesion	84 (60%)	37 (26.4%)	19 (13.6%)	140	< 0.0001
Low-grade tumor	38 (50.7%)	23 (30.7%)	14 (18.7%)	75	< 0.0001
High-grade tumor	33 (66%)	12 (24%)	5 (10%)	50	< 0.0001
Carcinoma in situ	13 (86.7%)	2 (13.3%)	0 (0%)	15	< 0.0001
Not evaluable specimen[a]	55 (25.1%)	11 (18%)	0 (0%)	66	< 0.0001

[a]Biopsy specimens inadequate for an accurate diagnosis

Table 3 Univariate and stepwise multivariate logistic regression model assessing the relationship of variables to diagnosis

	Univariate (crude OR)			Multivariate		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Size of specimen	1.95	(1.25, 3.04)	0.003			
Forceps						
BIGopsy	4.35	(1.30, 14.29)	0.018	3.42	(1.1, 11.74)	0.049
3F forceps	Ref.			Ref.		
Biopsy location						
Calyx	5.17	(1.18, 22.54)	0.048			
Pelvis	1.62	(0.82, 3.18)				
Ureter	Ref.					
Tumor size (mm)	0.99	(0.95, 1.05)	0.941			
Visible lesions						
Yes	3.55	(1.75, 7.19)	<0.001	2.63	(1.27, 5.26)	0.009
No	Ref.			Ref.		

Visible lesion: macroscopic lesion (papillary or sessile). Non-visible lesion: suspicious “flat” area

UTUC risk stratification is mandatory when using conservative treatment. CT urography, the most commonly used non-invasive imaging technique, has vastly improved the sensitivity and specificity for detection of UTUCs as compared with radiography alone [16]. Nevertheless, one study showed that CT urography accurately predicts the stage of disease in only 60% of patients [17]. In particular, CT urography falls short in its ability to reliably predict the stage or grade of tumors and to detect small lesions such as CIS [18]. The endourologic approach offers both visualization of UTUC lesions and performance of biopsies. It has greatly improved diagnostic accuracy and prognostic evaluation [9, 19]. Currently, URS biopsy is the most accurate means for grading (accurate grading is achieved in about 70% of cases) and possibly staging UTUC [10, 11]. Despite this, obtaining a sufficient and adequate specimen for pathological examination is still a challenge. Kleinmann et al. [20], comparing forceps vs. basket, found successful diagnosis in 63% vs. 94%, respectively ($p<0.0001$). Furthermore, among biopsies with a definite diagnosis of UTUC, specific grade was determined in 80% and 93% in the forceps and basket groups, respectively ($p=0.033$) [20].

The first purpose of this study was to determine which of the three more commonly used biopsy devices, 3F forceps, BIGopsy Backloading forceps, and 2.2F Nitinol basket, achieved better performance in terms of pathologic results, based on comparison of the diagnostic yield. We observed successful diagnosis in 236 (78.2%) samples, while 66 (21.8%) biopsy specimens were inadequate for an accurate characterization. Using the 3F forceps, the BIGopsy forceps and 2.2F Nitinol basket, a diagnosis was achieved in 74.9% (164/219 biopsies), 81.9% (50/61 biopsies), and 100% (22/22 biopsies) of cases, respectively. Of the 66 inadequate specimens, 55 (83.3%) were taken using 3F forceps and 11 (16.7%) using BIGopsy forceps. No cases of inadequate specimen arose when using the 2.2F Nitinol basket.

Forceps (either 3 Fr forceps or BIGopsy) are preferable for sampling smaller, sessile, or non-papillary lesions, while the basket can be used to debulk large papillary tumors by avulsing large pieces of tumor. These findings may be explained by the larger amount of tissue 4.3 (SD 1.9) mm, obtained with the basket. Furthermore, not all patients gave the consent to the use of three forceps for diagnosis. Therefore, in such cases, only the 3 Fr device was selected as the biopsy of choice, giving the fact that it is the most commonly used re-usable forceps.

Despite the difference between the three biopsy devices in obtaining a successful diagnosis of the specimen, none of them displayed superiority in terms of tumor staging.

At the multivariate logistic regression analysis, specimen size and visible lesions were found to be related to diagnosis. Univariate analysis revealed that, compared with the 3F forceps, BIGopsy forceps more often acquired samples from the calyx than from the ureter. The multivariate model showed BIGopsy forceps to be superior to the 3F forceps in terms of diagnostic ability (Table 3).

The second aim of the study was to evaluate the association between URS biopsy grading and final UTUC pathology results when distal ureterectomy or RNU was carried out. Clements et al. [8] reported a relationship between high URS biopsy grade and high final pathology specimen grade ($p<0.0001$). Williams et al. [21] reported a 75% agreement between biopsy grade and final pathology at RNU. The results of our study confirmed those in the literature. Tumor grade concordance was found in 19/28 (67.9%) cases while 9/28 (32.1%) were upgraded at final pathology. However, these nine cases upgraded at final pathology were tumors >20 mm in size (mean 36.3 mm) and, according to the EAU 2017 guidelines on UTUC [1], were not included in the conservative treatment protocol. The upgrading results could be related to the limitation of the biopsy device to obtain enough specimen tissue in large or mixed tumor for a definitive pathology result. In fact, the biopsy provides only pathological data about a well-defined area and, for this reason, in such cases it may misrepresent the entire tumor histological features. Despite the small series analyzed with this second aim ($n=28$), we did not find tumor upgrading when the lesion was less than 2 cm in size. To overcome these limitations in large lesion, new diagnostic tools such as the confocal laser endomicroscopy could be able to explore and characterize the entire surface of the lesion, distinguishing between low vs. high-grade UTUC. Furthermore, confocal laser endomicroscopy could potentially drive a correct biopsy in large and heterogeneous lesion [22].

These results suggest that the ideal method for diagnosis of UTUC is still missing. A decision on whether to treat conservatively a tumor or not has to be taken according to the characteristics of the tumor itself both on CT scan and URS aspect. The biopsy specimen has to be taken with large forceps whenever possible, to obtain the highest possible accuracy in grading the tumor.

Conclusions

With the current diagnostic devices, the ideal method is still missing. In our study, we found that BIGopsy forceps and the 2.2F Nitinol basket are superior to 3F forceps in obtaining an adequate specimen for the pathology examination and in achieving a successful diagnosis. For papillary lesions, the basket biopsy provides larger specimens in comparison to other biopsy devices described. For flat or sessile lesions, the BIGopsy forceps provide larger, deeper, and less distorted specimens than 3F forceps, which facilitates appropriate grade assessment. Concordance rate between URS biopsy grade and final pathology after distal ureterectomy or RNU is high for tumor < 2 cm in size.

Author contributions AB, AT protocol/project development. AT, FS, GB, JDS, HVR, OMF, JMG, JP data collection or management. AT, FS, GB, JDS data analysis.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Informed consent The research involved human participants obtaining informed consent.

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