The role of urinary cytology when diagnostic workup is suspicious for upper tract urothelial carcinoma but tumour biopsy is non-confirmatory

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Abstract

Introduction: We sought to determine the value of obtaining preoperative urinary cytology when diagnostic workup of an upper tract mass is suspicious for upper tract urothelial carcinoma (UTUC), but biopsy fails to confirm the diagnosis.

Methods: Using billing code data, 239 patients were identified as having undergone radical nephroureterectomy (RNU) by 16 urologists from September 29, 1998 to July 31, 2015. Of this group, 19 adult patients had a presumed preoperative diagnosis of UTUC in a native kidney, at least three months of followup, no history of concurrent radical cystectomy with RNU, and negative/non-diagnostic tissue biopsy. These patients were divided into three groups: Group A had no urinary cytology taken (n=6); Group B had upper and/or lower tract cytology performed with neither positive nor atypical (n=7); Group C had upper and/or lower tract cytology performed with at least one positive or atypical (n=6).

Results: Demographic information and diagnostic workup was similar between the groups, although Group A had more patients with a history of prior radical cystectomy for bladder cancer (p=0.02). One patient in Group B had benign tissue on final pathology. All patients in Groups A and C had malignancy on final pathology and overall, the three groups had similar rates of malignancy.

Conclusions: When a composite of clinical findings suggest UTUC, performing urinary cytology may not be necessary. A negative result in this setting should not be used to rule out UTUC, as this is often discordant with final pathology. A positive cytology result may help solidify the diagnosis when other findings are less clear.

Introduction

Intrarenal masses that are suspicious for upper tract urothelial carcinoma (UTUC) may be found either incidentally, during surveillance for bladder cancer, or after the development of symptoms such as flank pain or gross hematuria; however, obtaining a firm preoperative diagnosis may be challenging.

If a mass is noted on imaging studies, endoscopy may be performed, with the goal of visualizing the lesion and obtaining a tissue sample, either through cold-cup biopsy or brushings. However, endoscopy may be difficult and tissue samples may be challenging to obtain through ureteroscopes. In cases of a positive biopsy result, nephron-sparing approaches are generally preferred when complete tumour ablation is possible and tumours are low-grade, non-invasive, solitary, small, and easily accessible.[1] Otherwise, if the patient has normal renal function and is healthy enough to tolerate it, radical nephroureterectomy (RNU) with bladder cuff excision is the gold standard treatment.

In the setting of negative or non-diagnostic biopsy results, the differential diagnosis remains broad. When faced with this dilemma, some urologists will rely on urinary cytology (from the upper tract, lower tract, or both) to help solidify the diagnosis. When used for UTUC, it was reported to have a sensitivity of 45–64% and a specificity of 94–100%.[2-5]

Our group aimed to retrospectively study the outcomes of patients who have undergone RNU with negative or non-diagnostic preoperative tissue biopsy. Patients were divided into three groups based on the results of their cytology status: Group A had no urinary cytology taken; Group B had upper and/or lower tract cytology performed with results neither positive nor atypical; and Group C had upper and/or lower tract cytology performed with at least one positive or atypical result. These groups were then compared for demographic information, diagnostic workup, and final pathological results.

Methods

In the U.S., three billing codes are generally used to document the performance of RNU, as set by the American Medical Association: #50234, #50236, #50548. After obtaining institutional research subjects review board approval, a search of our billing database was performed using these billing codes spanning September 29, 1998 to July 31, 2015. This

system was initially launched on September 29, 1998 at our institution, and thus, was chosen as the start date of our study. This search generated a list of 239 such procedures performed by 16 surgeons who are part of the University of Rochester Urology Group (URUG).

All patients who underwent RNU by URUG for a presumed preoperative diagnosis of UTUC in their native kidneys with at least three months of followup were included. Patients must have had a negative or non-diagnostic tumour biopsy (endoscopic or percutaneous) or brushing. Patients who had RNU with concomitant cystectomy were excluded. A search of all patient records generated a list of 43 patients who did not meet these criteria and thus, were excluded due to: concomitant radical cystectomy (n=25), RNU for a non-functioning atrophic kidney (n=10), pediatric patient (n=4), procedure not matching billing code (n=2), RNU for extrinsic compression (n=1), or RNU in a transplant kidney (n=1).

Of the remaining patients, those with preoperative tissue samples that were positive, suspicious, or suggestive of malignancy were identified. This yielded 92 such patients and they were excluded from the study. Eighty-three patients did not undergo a preoperative biopsy and two patients had inadequate information in their charts to make this determination so they were also excluded. Three patients had endoscopic tissue samples showing only atypical urothelial or transitional cells of unknown significance. These biopsy results were considered "non-diagnostic," and thus, were included in the study.

The final study population comprised 19 patients who were divided into three groups. Group A had no urinary cytology taken (n=6); Group B had upper and/or lower tract cytology performed with neither positive nor atypical (n=7); and Group C had upper and/or lower tract cytology performed with at least one positive or atypical (n=6). The 19 patients were also rearranged into three different groups based on just their upper tract cytology: none (n=13), negative (n=2), and positive (n=4).

Kruskal-Wallis test was used to compare the medians of continuous variables in the three groups. For all categorical variables, Fisher's exact test was used, as the frequencies of events were quite small. All significance levels were set at 0.05. The statistical analyses were implemented with SAS 9.4 (SAS Institute Inc., Cary, NC, U.S.).

Of 239 patients who underwent RNU at our institution during the aforementioned time period, 72 patients had upper tract cytology taken preoperatively. When considering positive or atypical upper tract cytology as a "positive" test result and only UTUC (or carcinoma in situ [CIS]) as positive for the "condition of interest," the following performance characteristics were obtained: sensitivity 50/65 , 77% (95% confidence interval [CI] 0.67–0.87); specificity 4/7, 57% (95% CI 0.20–0.94); positive predictive value 50/53, 94% (95% CI 0.88–1.00); negative predictive value 4/19, 21% (95% CI 0.03–0.39). Here, cytology results were only considered if they were collected less than one year prior to their RNU.

Results

Demographic information is show in in Table 1. There were no statistically significant differences noted with regard to age,

Table 1. Demographic data and patient information

	Group A n=6	Group B n=7	Group C n=6	p
Age in years				
Mean (SD)	66.0 (9.4)	64.7 (12.6)	65.8 (18.3)	0.98
Gender, n (%)				
Female	4 (66.67)	2 (28.57)	2 (33.33)	0.51
Male	2 (33.33)	5 (71.43)	4 (66.67)	
ASA score, n (%)				
2	2 (33.33)	4 (57.14)	3 (50)	
3	3 (50)	2 (28.57)	3 (50)	0.92
4	1 (16.67)	1 (14.29)	0 (0)	
Medical comorbidities, n (%)				
HTN/DLD	5 (83.33)	4 (57.14)	3 (50)	0.60
DM	2 (33.33)	2 (28.57)	0 (0)	0.48
Moderate/severe CAD	2 (33.33)	2 (28.57)	1 (16.67)	1.00
Hepatic cirrhosis	0 (0)	1 (14.29)	0 (0)	1.00
Hypo/hyperthyroidism	0 (0)	3 (42.86)	0 (0)	0.08
Moderate/severe cardiac valve disease, CHF, or cardiomyopathy	1 (16.67)	2 (28.57)	0 (0)	0.74
Moderate/severe pulmonary disease	1 (16.67)	1 (14.29)	1 (16.67)	1.00
Moderate/severe cardiac dysrhythmia	3 (50)	0 (0)	1 (16.67)	0.08

ASA: American Society of Anesthesiology; CAD: coronary artery disease; CHF: congestive heart failure; SD: standard deviation; DLD: dyslipidemia; DM: diabetes mellitus; HTN: hypertension.

gender, American Society of Anesthesiology physical status classification system (ASA score), or medical comorbidities.

Diagnostic workup was also recorded and is shown in Table 2. Flank pain implies just flank pain without hematuria. There were no differences noted between the groups in patients with a history of bladder cancer (p=0.08); however, there was a difference noted in those having a history of cystectomy for bladder cancer (p=0.04). Group A had three such patients (50%) and none were noted in the other two groups.

None of the 19 patients in this study underwent percutaneous biopsy of their upper tract lesion prior to RNU. The three groups had similar endoscopic findings on visual inspection. Of the 19 patients, 12 had endoscopic exams demonstrating obvious sessile or papillary tumours (four such patients in each group). All 12 of these patients had malignant disease on final pathology.

Group A had two patients with stenotic areas at their ureteroileal anastomoses, but no obvious tumour on visual inspection. One of these patients was found to have CIS on final pathology. The other patient had high grade UTUC, pT4NxM1 with associated CIS, angiolymphatic invasion (ALI), and positive margins. This patient initially had antegrade brushings of the suspected lesion that revealed only "scant cellular material and artefactual change [precluding] definitive cytological evaluation." Preoperative imaging failed to reveal any evidence of metastatic disease.

One patient in Group B underwent ureteroscopy, which demonstrated a long proximal scarred area and a similar-looking area in the distal ureter. The patient initially presented with progressive left flank pain with obstruction noted on diuretic renal scintigraphy, progressive hydronephrosis, and thinning of the ipsilateral renal cortex. She also had gross hematuria with bloody efflux noted from her left ureteric orifice on cystoscopic examination. Brushings of the concerning area read: "atypical cells of urothelial type are present." Upper tract washings for urinary cytology were not performed in this patient and lower tract cytology was negative. Final pathology after RNU was benign fibrotic stricture.

Two other patients in this group had inadequate endoscopic examinations, as the areas of interest could not be properly examined due to technical challenges. Biopsies +/- brushings were taken under flouroscopic guidance. Both of these patients had high-grade UTUC (one was pT3N2M0, the other was pT2N0M0).

In Group C, two patients had equivocal endoscopic findings. One had a "shaggy, irregular area" and final pathology read pTaN0M0 low-grade UTUC. The other patient had endoscopy demonstrating only blood clots and a dilated

Table 2. Diagnostic workup of patients with masses suspicious for UTUC

	Group A n=6	Group B n=7	Group C n=6	p
Mode of presentation, n (%)				
Gross hematuria	3 (50)	3 (42.86)	4 (66.67)	
Flank pain	0 (0)	4 (57.14)	1 (16.67)	0.15
Incidental finding	2 (33.33)	0 (0)	1 (16.67)	
Followup for bladder cancer surveillance	1 (16.67)	0 (0)	0 (0)	
History of bladder cancer, n (%)				
None	3 (50)	7 (100)	5 (83.33)	
Concurrent	0 (0)	0 (0)	0 (0)	
Prior	3 (50)	0 (0)	1 (16.67)	0.08
History of cystectomy for bladder cancer, n (%)	3 (50)	0 (0)	0 (0)	**0.04**
Side of lesion, n (%)				
Left	4 (66.67)	5 (71.43)	3 (50)	0.84
Right	2 (33.33)	2 (28.57)	3 (50)	
Endoscopic findings				
Grossly positive for tumour	4 (66.67)	4 (57.14)	4 (66.67)	1.00
Equivocal/unable to properly visualize	2 (33.33)	3 (42.86)	2 (33.33)	
Method of biopsy, n (%)				
Endoscopic biopsy	5 (83.33)	5 (71.43)	5 (83.33)	1.00
Percutaneous biopsy	0 (0)	0 (0)	0 (0)	
Endoscopic brushing	1 (16.67)	2 (28.57)	1 (16.67)	
Biopsy result, n (%)				
Negative	5 (83.33)	4 (57.14)	2 (33.33)	0.39
Non-diagnostic	1 (16.67)	1 (14.29)	3 (50)	
Atypical cells	0 (0)	2 (28.57)	1 (16.67)	

UTUC: upper tract urothelial carcinoma.

proximal ureter with no other clear visual evidence of tumour. Her final pathology yielded a pT1N0M0 low-grade UTUC.

Final pathology of RNU specimens are shown in Table 3. All patients in Groups A and C had malignant disease noted on final pathology, and as noted, one patient in Group B had benign disease.

Three patients in this series had positive margins, one in each group. The patient in Group B had tumour present at a deep ureteral soft tissue margin, in peripelvic and periureteral adipose tissue, and there were metastatic deposits in 3/19 lymph nodes. The patient in Group C had CIS involving the renal pelvis and ureter that extended to the ureteral margin of resection (bladder cuff). The third patient (Group A) was mentioned above.

The 19 patients in our series were rearranged and divided in to three new groups based only on the status of their upper tract cytology: none (n=13), negative (n=2), and positive (n=4). The single patient noted above with benign final pathology had no upper tract cytology taken. Upon comparing the three new groups based solely on final pathology (benign or malignant), no differences were noted between the groups (p=1.00).

Discussion

Urologists will often biopsy upper tract masses that look suspicious for UTUC in an attempt to confirm visual evidence of disease. When these results are positive, they are gen-

Table 3. Final pathology of RNU specimens

	Group A n=6	Group B n=7	Group C n=6	p
Neoplasm, n (%)				
Malignant	6 (100)	6 (85.71)	6 (100)	1.00
Benign	0 (0)	1 (14.29)	0 (0)	
Histology, n (%)				
UC	5 (83.33)	6 (85.71)	5 (83.33)	1.00
CIS	1 (16.67)	0 (0)	1 (16.67)	
Fibrotic stricture	0 (0)	1 (14.29)	0 (0)	
Grade, n (%)				
High	6 (100)	5 (83.33)	4 (66.67)	0.74
Low	0 (0)	1 (16.67)	2 (33.33)	
pT stage, n (%)				
a	0 (0)	1 (16.67)	1 (16.67)	
is	1 (16.67)	0 (0)	1 (16.67)	
1	1 (16.67)	1 (16.67)	2 (33.33)	0.84
2	2 (33.33)	1 (16.67)	0 (0)	
3	1 (16.67)	3 (50)	1 (16.67)	
4	1 (16.67)	0 (0)	1 (16.67)	
pN, n (%)				
x	3 (50)	2 (28.57)	1 (16.67)	
0	3 (50)	4 (57.14)	3 (50)	0.47
1	0 (0)	0 (0)	2 (33.33)	
2	0 (0)	1 (14.29)	1 (16.67)	
pM, n (%)				
0	5 (83.33)	7 (100)	6 (100)	0.63
1	1 (16.67)	0 (0)	0 (0)	
Associated CIS, n (%)				
No	2 (33.33)	3 (42.86)	3 (50)	1.00
Yes	3 (50)	3 (42.86)	2 (33.33)	
N/A	1 (16.67)	1 (14.29)	1 (16.67)	
Angiolymphatic invasion, n (%)				
No	2 (33.33)	5 (71.43)	3 (50)	0.44
Positive/suspicious	3 (50)	2 (28.57)	1 (16.67)	
N/A	1 916.67)	0 (0)	2 (33.33)	
Margin, n (%)				
Positive	1 (16.67)	1 (14.29)	1 (16.67)	1.00
Negative	5 (83.33)	6 (85.71)	5 (83.33)	

Grade: Group B missing 1 (benign, thus no grade). CIS: carcinoma in situ; RNU: radical nephroureterectomy; UC: urothelialcarcinoma.

erally considered confirmatory and add evidence supporting a decision to perform RNU. When they return as either negative or non-diagnostic, one must question whether the sample was taken from the lesion itself and also whether it was destroyed during specimen retrieval or processing.

It is the fear of this scenario that will often drive a urologist to obtain urinary cytology; however, results can be misleading, especially when visual evidence is strong. To our knowledge, this is the first study looking at the utility of performing urinary cytology when endoscopic results are positive, but biopsy results are negative or non-diagnostic.

Several other studies have been conducted looking at the operative characteristics of urinary cytology following RNU.[4,6] Others have performed studies to determine if positive urine cytology can predict outcomes following RNU for UTUC.[7-9] While these groups have demonstrated correlations between positive cytology and the presence of disease, they did not take into account biopsy information. We feel that this patient population deserves special attention, as patients with positive biopsies will likely undergo radical therapy regardless of cytology results.

In our study, atypical cytology was grouped with positive cytology because we feel that such results are often considered clinically positive when deciding on management options, especially when the rest of the diagnostic workup is suspicious. Chen et al have previously found that 8/19 (42%) of patients who had atypical upper tract cytology had UTUC on followup biopsy or postoperative specimen.[10]

Only one patient in our series had benign disease on final pathology. This patient had negative lower tract cytology (Group B) and one can see that this was concordant with the negative pathology result. Had her surgeon made the decision to observe this lesion rather than operate, this patient may have been spared radical surgery; however, if this same logic were applied to the entire group, then 6/7 patients (85.7%) would have received an inappropriate treatment for malignant disease.

This patient was one of 13 who did not have upper tract cytology performed and one may argue that if she had, a negative result may have spared her an unnecessary RNU. That said, the other 12 patients in this group (92.3%) had malignant disease despite the absence of upper tract cytology. In addition, 2/2 patients (100%) who had negative upper tract cytology had malignant disease on final pathology.

This is a retrospective review of a very small number of patients in a single institution, which, when investigating performance of cytology, is a real issue, especially given the technical and expert issues with interpreting the results. Furthermore, since all patients eventually underwent RNU, one can infer that these patients all had a relatively high pre-RNU probability of harbouring malignancy. It is also likely that there were some patients seen by URUG during this time period who had suspicious upper tract lesions and negative cytology who never went on to receive RNU.

Patients in Group A had a higher incidence of prior cystectomy and urinary diversions. A history of cystectomy is a clear risk factor for the development of UTUC and one meta-analysis found the prevalence in this setting to be 0.75–6.4%.[11] Thus, an upper tract defect on imaging is more likely to raise clinical suspicious of UTUC in patients with this history. As such, these patients may have been more likely to undergo RNU despite their cytology status or lack thereof.

The small number of patients in each group makes it difficult to draw definitive conclusions from a statistical perspective; however, only one of 19 patients in the entire series had discordant final pathology and we feel that this is a very interesting finding, even if taken from a purely qualitative outlook.

Conclusion

Obtaining urinary cytology may not be necessary when there is a very high degree of clinical suspicion for UTUC, even in the absence of a positive tissue biopsy. This may be based on a composite of clinical findings, including imaging studies, endoscopy, initial presentation, and clinical history. In this setting, a negative cytology result is often discordant with final pathology and thus, should not be used to rule out the possibility of malignancy. When there is considerable doubt as to the malignant potential of these masses, a positive cytology result may help reaffirm the decision to perform radical surgery.

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