The merits of cytology in the workup for upper tract urothelial carcinoma – a contemporary review of a perplexing issue

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ABSTRACT

Introduction: The importance of upper tract cytology for evaluating tumors is unclear. We correlated upper tract cytology with histologic findings in patients who underwent nephroureterectomy for upper tract urothelial carcinoma (UTUC) at a single tertiary care referral center.

Materials and Methods: 137 patients underwent nephroureterectomy between 2004 and 2012. 18 patients were excluded (benign tumors, atrophic kidneys with the remaining 119 patients serving as our study population). Upper tract cytology from the renal pelvis and/or ureter were retrospectively reviewed and analyzed with final pathology data in the remaining patients with UTUC.

Results: 57% (68/119) had preoperative upper tract cytology collected. 73% (50/68) patients had abnormal cytology (positive, suspicious) with a sensitivity of 74% (which increased to 90% if atypical included), specificity of 50% and a positive predictive value of 98%. High grade tumors were more common than expected (77% high grade vs. 20% low grade). Abnormal cytology did not predict T stage or tumor grade. Interestingly, positive upper tract cytology was found in all of the UTUC CIS specimen.

Conclusions: Upper tract cytology has been utilized to support the diagnosis of upper tract urothelial carcinoma. Our data demonstrates that abnormal cytology correlates well with the presence of disease but does not predict staging or grading in these respective patients.

INTRODUCTION

Upper tract urothelial carcinoma (UTUC) is uncommon, representing less than 5% of urothelial tumors. The standard workup for UTUC includes upper tract imaging (either cross-sectional or retrograde pyelogram), upper tract (selective) cytology (UTC) and possible ureteroscopy with tumor biopsy. Endoscopic management is an acceptable option for low grade and smaller tumors, especially in patients where nephron sparing is an imperative indication (i.e. patients with renal insufficiency or multiple comorbidities). These patients can be treated either by a retrograde or an antegrade approach, depending on tumor size, location and accessibility. To appropriately select these candidates, a thorough workup is required which yields reliable information regarding location, size, stage, and grade of the tumor.

Despite advances in technology, diagnosis of upper tract tumors continues to be challenging and often times biopsy is inconclusive or not performed due to the difficulty of reaching the lesion of concern. The sensitivity of UTC has been reported to be 64-71% (1-4), which is higher when compared to voided urine cytology (VUC) which is sometimes utilized for upper tract diagnostic evaluation. Messer and associates reported their

outcomes in 2010, looking at both voided urinary cytology and selective UTC. The sensitivity of selective UTC was 71% and 78% for detecting high grade disease and muscle invasive disease, respectively. They concluded that urinary cytology in isolation lacked performance characteristics to accurately predict invasiveness and grade of UTUC (2).

The purpose of this study is to investigate the diagnostic performance of UTC in patients with UTUC.

MATERIALS AND METHODS

A retrospective chart review of all patients who underwent a radical nephroureterectomy (RNU) at a single institution between 2004 and 2012 was performed. One-hundred-thirty-seven patients were identified in our IRB approved institutional database and 18 of them were excluded. The patients who were excluded had undergone surgery revealing benign pathology (benign tumors, chronic infection, atrophic kidneys). Upper tract cytology from the renal pelvis and/or the ureter were reviewed and correlated with final pathology data. The specimens were selectively collected with an open end catheter under fluoroscopic guidance from the tumor side. A minimum of 3-5mL of sterile saline was used to wash (barbotage) 3-5 times on average, before the retrograde pyelogram was performed. The washing was done by 3 experienced urologic oncologists, supervising fellows and residents in training. The specimens were sent fresh to pathology, where they were centrifuged and the supernatant was poured off and vortexed to resuspend the cell pellet. CytoLyt solution was added and the specimen was centrifuged again. The supernatant was poured off and 1-2 drops of the pellet were added to the PreservCyt solution. After 15 minutes the specimen was run on a Thinprep processor and the slide was stained with modified Papanicolau staining method and coverslipped to be screened.

The cytology results were reported as being positive, suspicious, atypical, reactive or benign and the histology was staged and graded according to the American Joint Committee of Cancer AJCC/TNM staging and 2004 World Health Organization/International Society of Urologic Pathology (WHO/ISUP) grading systems. No particular classification scheme for urine cytology has been followed by the cytopathologists. Positive and suspicious cytologies were defined as abnormal, but atypical and reactive were defined as benign.

The sensitivity, specificity and positive predictive values were calculated using Microsoft® Excel software (version 2007). We used the Student's t-test to compare means of groups and the Fisher exact test was used to compare proportions.

RESULTS

A total of 119 patients were submitted to RNU for UTUC at a mean age at diagnosis of 70 years (range 42-90 years). Muscle invasive tumors were found in 52 (44%) of 119 patients and interestingly these tumors were more prominent in patients who did not have an upper tract cytology collected as a part of their workup when compared to the patients who did (51% (26/51) vs. 38% (26/68), P = 0.08), although this finding was not statistically significant. Age did not affect the tumor stage and muscle invasive disease was seen in 41% of patients less than 65 years compared to 44% of those greater than 65 years (P = 0.39). Sixty-eight patients (57%) had UTC collected as a part of their preoperative workup and 73% of the specimens were abnormal. No difference was noted between males and females except that the disease was more prevalent amongst males (70% versus 30%, p < 0.002) (Table-1). Table-2 demonstrates the correlation of UTC with final pathological tumor stage. Five patients had CIS and all of them had positive UTC.

The sensitivity and specificity of UTC were 74% and 50% with a positive predictive value of 98%, respectively. Abnormal UTC did not predict tumor stage or grade. Abnormal cytology was found in 74.5% of the high grade tumors compared to 73% of the low grade tumors (P = 0.26) (Figure-1). High grade tumors were more common than low grade tumors (79% vs. 21%, P < 0.001) and this proportion was independent of cytology results (positive (76%), suspicious (75%), atypical (73%) and benign (72%) (Table-3). Thirty-one (72%) of 43 superficial compared to 19 (76%) of 25 muscle invasive tumors were associated with abnormal UTC (p = 0.36) (Figure-2).

Table 1 - Characteristics of the eligible patients.

	Male (%)	Female (%)	P – value
Number	83 (70)	36 (30)	
Age, years (mean)	69	72.6	0.1
Tumor stage			
T0	1 (1.2)	1 (2.7)	0.52
Ta	27 (32.5)	10 (27)	0.67
Tis	2 (2.4)	3 (8.3)	0.16
T1	16 (19.3)	7 (19.4)	1.00
≥ T2	37 (44.6)	15 (41.7)	0.38
Tumor grade			
HG	66 (79.5)	28 (77.8)	0.42
LG	17 (20.5)	8 (22.2)	0.42
Upper tract cytology available	47 (56.6)	21 (58.3)	0.43
Abnormal	36 (76.6)	14 (66.7)	0.19
Atypical	8 (17)	3 (14.3)	1.00
Benign	3 (6.4)	4 (19)	0.19

Table 2 - Correlation of UTC with tumor stage and grade.

	Upper Tract Cytology		
	Abnormal (%)	Benign (%)	P - value
T0	1 (2)	1 (5)	0.48
Ta	17 (34)	5 (26)	0.77
CIS	5 (10)	0 (0)	0.31
T1	8 (16)	6 (32)	0.19
T2	5 (10)	3 (16)	0.68
T3	11 (22)	4 (21)	1.0
T4	3 (6)	0 (0)	0.56
High Grade	38 (76)	13 (68)	0.55
Low Grade	11 (22)	5 (26)	0.75
Other*	1 (2)	1 (5)	0.48

*Two specimen were T0 and one undifferentiated large cell tumor
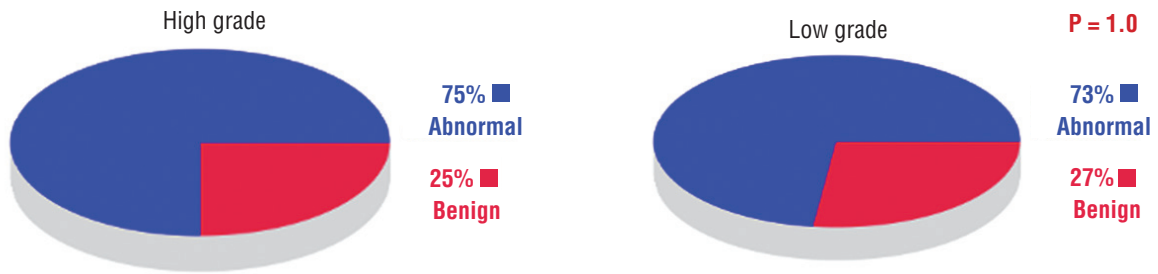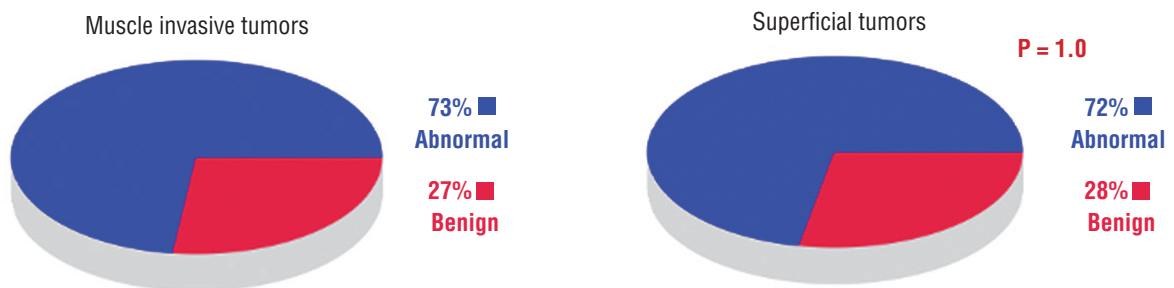
Figure 1 - UTC and tumor grade.

Table 3 - UTC and tumor grade.

Upper tract cytology				
	Positive(%)	Suspicious(%)	Atypical(%)	Benign(%)
High Grade	32(76)	6(75)	8(73)	5(72)
Low Grade	9(21)	2(25)	3(27)	1(14)
Other*	1(3)			1(14)

* Two specimen were T0 and one undifferentiated large cell tumor

Figure 2 - UTC and tumor stage.

DISCUSSION

The diagnosis of UTUC can be difficult and upper tract selective cytology has been utilized to support the diagnosis of disease presence. With advancement in technology and better understanding of the pathogenesis of UTUC, the role of endoscopic management has become a more popular treatment option, especially in patients with solitary kidneys, impaired renal function and in patients with multiple comorbidities who are at higher risk during prolonged and more extensive surgeries. Accuracy in diagnosis is therefore especially important and better diagnostic tools may be needed.

According to our study, 73%, of patients who underwent RNU for UTUC had abnormal UTC with a calculated sensitivity and specificity of 74% and 50%, respectively. The low specificity may be explained by various reasons, for example, lower stage and grade tumors, which may be less prone to shedding tumor cells into the collecting system, or sampling error. Skolarikos et al. evaluated 62 patients who were treated for UTUC and underwent an ureteroscopic biopsy and/or collection of UTC as a part of their preoperative workup. Only 40% (19/48) of their patients had positive/suspicious UTC but their data demonstrated that positive cytology predicted high grade tumors in 14 (67%) of 21 cases. They also demonstrated improved sensitivity and specificity of detecting high grade UTUC by combining biopsy results and upper tract cytology. The sensitivity and specificity increased from 43% to 55% and from 23% to 85%, respectively. Their biopsy grade correlated well with tumor invasiveness. None of the 6 specimens with biopsy grade 1 compared to 11 of 13 with grade 3 were found to be muscle invasive (5).

A more recent retrospective study by Williams et al. showed a higher prediction rate and correlation with tumor stage of positive upper tract cytology in patients who underwent a nephroureterectomy for UTUC. They correlated UTC with histologic findings and 21 (70%) of 30 specimens were positive. Positive UTC was associated with high grade tumors (82%) and predicted stage pT1 or greater in 15 (75%) of 20 cases (6).

Straub and associates investigated the accuracy of upper tract cytology and ureteroscopic biopsy in predicting the correct tumor grade in patients with UTUC. Their data showed the sensitivity of cytology and biopsy to be 64% and 74%, with a combined sensitivity of 84%. The accuracy of cytology in predicting high grade tumors was 53% which improved to 68% when combined with biopsy results and more importantly 15% of high grade tumors were misinterpreted as being low grade (3). Our findings show that abnormal UTC correlates with the presence of UTUC and was found in 73% of the patients but it did not predict tumor stage or grade whi-

ch is contrary to prior studies. Interestingly, all of the CIS specimens had positive UTC, but the number (N = 5) was too low to reach statistical significance. Our study also demonstrates that superficial upper tract tumors were as likely to have abnormal cytology as muscle invasive tumors (72% of superficial and 76% muscle invasive tumors) which emphasizes the importance of combining all preoperative data (cytology, cross--sectional imaging, ureteroscopic findings and biopsy results) when making a decision if endoscopic surgery is a suitable therapeutic option. Xu et al. demonstrated higher sensitivity with VUC in combination with fluorescence in situ hybridization analysis (FISH) for detecting upper tract tumors with an overall sensitivity 85.9% compared to 45.1% for VUC and 78.9% for FISH (4). Table-4 summarizes published studies focusing on diagnostic utilities of UTC.

The present study has some limitations including its retrospective design and the inherent selection bias for patients to undergo a nephroureterectomy and therefore more likely to have higher grade and more advanced disease which may not accurately reflect all patients treated at outside institutions. Moreover, the urine cytology was not routinely graded, and therefore we were unable to correlate the grade of the positive cytology with final pathology.

CONCLUSIONS

The diagnosis of UTUC may be challenging and according to our data, selective cytology correlates with the presence of urothelial carcinoma but does not accurately predict the stage or grade of these respective tumors. At present, UTC is one of the more important diagnostic tools to work up upper tract tumors and should be used in conjunction with other diagnostic modalities and clinical findings whenever technically possible. The continual goal for novel biomarkers of diagnostic, therapeutic, and prognostic utility remains a mainstay of current research efforts.

CONFLICT OF INTEREST

None declared.

Table 4 - Summary of published studies.

Study	Number	Sensitivity (%)	Specificity (%)	PPV (%)	Accuracy of bx predicting high grade
Raica (7)	34	97	-	-	-
Keeley (8)*	28	82	-	-	-
Messer (2)**	168	71	-	53	-
Williams (6)	30	70	-	-	75%
Skolarios (5)	48	40	-	-	High****
Highman (9)	24	58	-	-	-
Xu (4)***	71	86	97.8	-	-
Straub (3)	77	64	-	-	58%
Our study	68	74	50	98	-

* Additional washes obtained after a biopsy was performed
** Only high grade disease
***Voided cytology and FISH combined
****Biopsy grade 3 predicted grade 3 in 12/13 (92%)

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