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Outcome of Patients with Abnormal Upper Tract Cytology and Negative Initial Workup

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ABSTRACT

INTRODUCTION: Patients with pathologically confirmed upper tract transitional cell carcinoma (TCC) currently undergo surveillance according to well described protocols. The literature offers little guidance for monitoring patients with abnormal upper tract cytology without prior upper tract TCC. The purpose of the present study was to assess the risk of upper tract TCC based on cytology and determine a reasonable observation strategy for this abnormal finding.

METHODS: The authors performed a 10-year retrospective cohort study of 204 patients (366 renal units) within the New England Veterans Administration Healthcare System. Upper tract cytology was collected: (1) as a consequence of lateralizing hematuria during cystoscopy in 2 patients; (2) following abnormal upper tract imaging in 27 patients; (3) from the bladder in the presence of a suspected bladder tumor and/or carcinoma in-situ (CIS) in 16 patients; (4) from the bladder despite a negative workup for lower tract tumor in 159 patients. Cytology results reported as negative or atypical were categorized as normal; suspicious or positive results were categorized as abnormal. Odds ratios (OR) were calculated and hazard curves plotted to determine risk and time span of tumor development among the cohorts.

RESULTS: Twenty-six renal units had upper tract TCC over a median follow up of 38 months. The OR for development of upper tract TCC with abnormal upper tract cytology was 3.27 and did not change with a previous history of lower tract disease. The accumulation rate differed with normal and abnormal upper tract cytology among those who developed upper tract TCC.

CONCLUSIONS: Upper tract cytology has a poor sensitivity for tumors of the upper urinary tract. Patients with abnormal upper tract cytology are 3 times more likely to develop TCC than patients with normal upper tract cytology and should be carefully monitored for at least 6 years. However, the exact method and frequency of monitoring remains undetermined.

KEYWORDS: Transitional cell carcinoma; Urothelial carcinoma; Cytology; Upper tract; Renal pelvis; Ureter

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INTRODUCTION

Transitional cell carcinoma (TCC) involves the upper urinary tract (calyces, renal pelvis, and ureter) in 5% of cases [1]. Surveillance protocols for patients with previously pathologically confirmed upper tract urothelial tumors are well established and incorporate the use of upper tract cytology and imaging [2-4]. However, in the event that upper tract cytology is abnormal without overt evidence of tumor, no defined algorithms exist.

Current standards of care dictate acquisition of upper tract cytology in the event of lateralizing hematuria emanating from the ureteral orifice at the time of cystoscopy, abnormal upper tract imaging suggestive of TCC, or nonlocalized abnormal cytology collected from the bladder. In the upper tract, cytology is known to be fairly specific but lacking in sensitivity [5]. Thus, finding abnormal upper tract cytology often precedes further diagnostic workup with ureteropyeloscopy, which enables direct visualization and biopsy of any suspicious lesions [6]. Ureteropyeloscopy has now become the gold standard as a diagnostic modality, although it is not without risk. Unfortunately, ureteropyeloscopy does not always yield identification of macroscopic lesions. Therefore, the present authors have questioned the diagnostic yield of ureteropyeloscopy in cases of isolated abnormal upper tract cytology. Also unclear is the likelihood of developing an upper tract tumor after having an abnormal upper tract cytologic specimen in the absence of a tumor.

The purpose of the present retrospective investigation was to analyze patients with abnormal upper tract cytology (1) to determine the likelihood and time span of upper tract TCC development after finding an abnormal upper tract cytology specimen and (2) to develop a reasonable, safe, and economical strategy to monitor at-risk patients for upper tract urothelial tumor development.

METHODS

Approval for the study was granted by the Institutional Review Board of the Veterans Administration (VA). Data were retrospectively collected on all patients who had upper tract cytology studies within the New England VA Health Care System (Boston MA, Togus ME, Manchester NH, Providence RI) from 1997 to 2007.

The authors identified 204 appropriate patients with 366 renal units (including renal parenchyma, renal pelvis, and ureter). The diagnosis of upper tract TCC was based on a pathologic specimen from nephroureterectomy, ureterectomy, or biopsy, or from endoscopic visualization of a tumor at the time of ablation.

Upper tract cytology was collected: (1) as a consequence of lateralizing hematuria during cystoscopy in 2 patients; (2) following abnormal upper tract imaging in 27 patients; (3) from the bladder in the presence of a suspected bladder tumor and/or carcinoma in-situ (CIS) in 16 patients; (4) from the bladder despite a negative workup for lower tract tumor in 159 patients. Cytology was dichotomized as *normal* (negative or atypical) or *abnormal* (suspicious or positive), which is how the authors consider patients in determining treatment plans.

To determine the likelihood of upper tract tumor development based on upper tract cytology, risk estimates were computed using a two-sided Fischer exact test. Odds ratios (OR) were also calculated after correcting for previous lower tract TCC and/or CIS using the Mantel-Haenszel test. To establish the time span for tumor development, Kaplan-Meier hazard analyses were computed for renal units with normal and abnormal upper tract cytology. The Cox proportional hazard procedure was utilized to enter covariates into the model. Groups were compared using a log-rank (Mantel-Cox) chi-square test.

RESULTS

Of the 366 renal units studied, 166 (45.4%) had normal and 200 (54.6%) had abnormal upper tract cytology (Table 1). Among the renal units with normal upper tract cytology, the method of collection included a lavaged specimen in 137 (82.5%), a brushed specimen in 6 (3.6%), an aspirated specimen in 10 (6%), and unknown in 13 (7.8%). Among the renal units with abnormal upper tract cytology, the method of collection included a lavaged specimen in 170 (85%), a brushed specimen in 11 (5.5%), an aspirated specimen in 10 (5%), and unknown in 9 (4.5%).

Table 1. Comparison of Upper Tract Tumor Development in Renal Units with Normal and Abnormal Cytology.

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Upper Tract Cytology	Normal		Abnormal	
	n	% n	n	% n
Renal units studied (n = 366)	166	45.4	200	54.6
Renal units with TCC (n = 26)	7	26.9	19	73.1
Proportion of renal units with tumors				
Normal (n = 166)	7[a]	4.2	---	---
Abnormal (n = 200)	---	---	19[b]	9.5

Abbreviation: TCC, transitional cell carcinoma
[a]All present at time of initial cytology
[b]15 present at time of initial cytology; 4 developed later

Table 2. Corresponding Pathologic and Cytologic Data on All Renal Units Diagnosed With Upper Tract Tumors. doi: 10.3834/uij.1944-5784.2009.12.01t2

Renal Unit	UT Cytology	Collection	Stage/ Grade	UT Location	LT Tumors	Diagnosis
1	Abnormal (positive)	Lavage	T2G2	Renal pelvis	TaG2	Nephro-U
2	Abnormal (suspicious)	Lavage	T1G2	Distal ureter	TaG2	Ureterectomy
3	Abnormal (positive)	Brush	T3HG	Renal pelvis	T1G3 + CIS	Nephro-U
4	Normal (negative)	Lavage	T2	Renal pelvis	None	Nephrectomy
5	Abnormal (positive)	Brush	T3G3	Renal pelvis	None	Nephro-U
6	Abnormal (suspicious)	Lavage	T3HG	Renal pelvis	None	Nephro-U
7	Normal (atypical)	Brush	TaG2	Renal Pelvis	TaLG	Nephro-U
8	Abnormal (positive)	Brush	LG	Pelvis & ureter	T1G2	Nephro-U
9	Abnormal (positive)	Brush	T1LG	Renal pelvis	T1LG	Partial nephrectomy
10	Normal (negative)	Unknown	T4G3	Renal pelvis	None	Nephro-U
11	Abnormal (suspicious)	Brush	TaLG	Renal pelvis	T1G2	Urs
12	Abnormal (suspicious)	Lavage	T1HG	Renal Pelvis	CIS	Nephro-U
13	Abnormal (suspicious)	Unknown	TaG1-2	Renal pelvis	T1G2-3 + CIS	Nephro-U
14	Normal (atypical)	Brush	T1G1	Distal ureter	TaG1-2	Nephro-U
15	Abnormal (suspicious)	Unknown	TaLG	Renal pelvis	T1G1 + CIS	Nephro-U
16	Abnormal (suspicious)	Brush	T2G3	Renal Pelvis	None	Nephro-U
17	Abnormal (suspicious)	Unknown	TaG1	Pelvis & ureter	T1G2	Nephro-U
18	Abnormal (suspicious)	Unknown	TaLG	Ureter	T1G2	Ureterectomy
19	Normal (negative)	Brush	T1G2	Distal ureter	T1G2	Urs
20	Normal (atypical)	Lavage	T1G2	Renal pelvis	TaLG	Nephro-U
21	Abnormal (suspicious)	Lavage	TaG2	Renal pelvis	TaG2	Nephro-U
22	Abnormal (positive)	Lavage	T2	Renal pelvis	T2G3	Nephro-U
23	Abnormal (suspicious)	Lavage	TaLG	Renal pelvis	TaG1	Nephro-U
24	Normal (negative)	Lavage	T2a	Distal ureter	T1G3 + CIS	Ureterectomy
25	Abnormal (suspicious)	Brush	T1G1/ T3G3	Pelvis & ureter	None	Nephrectomy and ureterectomy
26	Abnormal (positive)	Lavage	T2G2	Renal pelvis	None	Nephro-U

Abbreviations: UT, upper urinary tract; LT, lower urinary tract; Urs, ureteropyeloscopy; Nephro-U, nephroureterectomy

The average follow-up was 33.2 months (range, < 1 – 118 months) after initial cytology collection for patients with normal upper tract cytology and 38 months (range, < 1 – 157 months) after initial cytology collection for patients with abnormal upper tract cytology. The average follow-up for patients with upper tract TCC was 35.6 months.

Twenty-six renal units had upper tract TCC. Seven of the 26 (26.9%) renal units had normal upper tract cytology and 19 of 26 (73.1%) had abnormal upper tract cytology (Table 1). Table 2 illustrates the relevant characteristics of each renal unit diagnosed with upper tract TCC including the corresponding upper tract cytology, collection method, tumor stage/grade, tumor location, method of diagnosis, and corresponding history of lower tract tumors.

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Figure 1. Upper tract (UT) TCC Diagnosis as a Function of Time With Normal or Abnormal UT Cytology.
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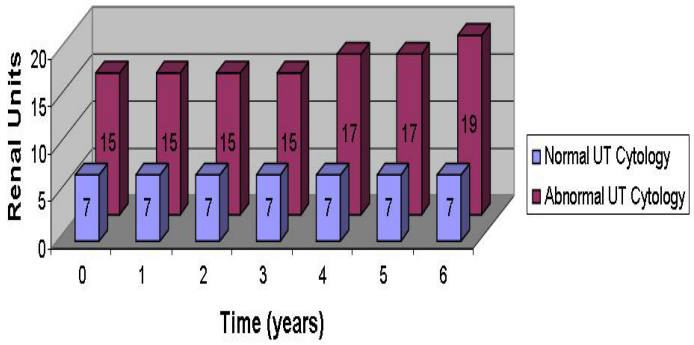


The OR for development of upper tract TCC with abnormal versus normal upper tract cytology was 3.27 (95% confidence interval {CI}, 1.27-8.39; *P* = .01). The OR did not change when controlling for presence or absence of previous lower tract TCC and/or CIS. The OR for development of upper tract TCC with abnormal upper tract cytology but no previous lower tract TCC and/or CIS was 3.34 (95% CI, 0.66-17.01; *P* = .02). The OR for development of upper tract TCC with abnormal upper tract cytology and with previous lower tract TCC and/or CIS was 3.22 (95% CI, 1.01-10.25; *P* = .05).

Among the 26 renal units diagnosed with upper tract tumor, all 7 with normal upper tract cytology presented with a tumor at the time of initial work up and none developed a tumor during follow-up. However, among the renal units with a tumor and abnormal upper tract cytology, 15 presented with a tumor at the time of initial cytology collection and 4 additional renal units developed a tumor over 6 years for a total of 19 renal units with a tumor (Table 1; Figure 1). Furthermore, Kaplan-Meier hazard curves were generated to establish the time span for tumor development in renal units with normal and abnormal upper tract cytology. The rate of tumor development differed for renal units with normal and abnormal upper tract cytology (Figure 2). The rate of tumor development was not affected by the presence or absence of previous lower tract TCC and/or CIS (Figure 3).

DISCUSSION

Urothelial tumors of the upper urinary tract can present diagnostic problems. There are protocols for surveillance of upper tract TCC after endoscopic treatment [2-4], but there are limited data on the long-term follow-up for patients with abnormal upper tract cytology in the absence of a tumor. There are no protocols describing how to follow patients with abnormal upper tract cytology because it is unclear what risk this finding produces.

Ureteropyeloscopy aids in the diagnosis by enabling direct visualization of lesions and, potentially, biopsy for tissue diagnosis [6,7]. Disadvantages of ureteropyeloscopy include the need for anesthesia, occasional inability to access the upper urinary tract, inability or difficulty in inspecting the entire urothelial surface, ureteral perforation or avulsion, and postoperative ureteral stenosis/stricture. Furthermore, some patients have abnormal cytology with no other evidence of macroscopic disease. For these patients, ureteropyeloscopy is an unnecessary procedure.

The authors of the present study sought to answer some basic questions regarding the follow-up of patients with abnormal upper tract cytology. More specifically, how aggressively and for how long do these patients need to be followed? The following questions were addressed.

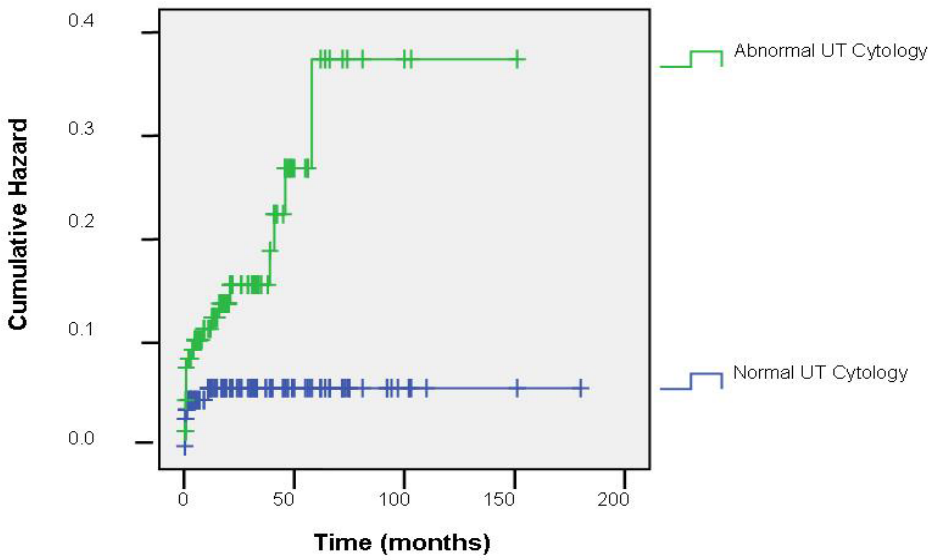
What are the chances of developing upper tract urothelial carcinoma after finding abnormal upper tract cytology?

The majority of the renal units studied had upper tract cytology collected by a blind lavage at the time of retrograde ureteropyelogram. The purpose of the evaluation was to localize an abnormal voided cytology in the absence of lower tract pathology. This may explain the consistency with previous investigators who reported a low sensitivity and high specificity of upper tract cytology. Upper tract cytology can be collected by various techniques (aspirated, lavaged, or brushed) and from different locations along the length of the upper tract (renal pelvis to distal ureter) [8-12]. The technique used may vary based on clinician and clinical situation, which can significantly affect sensitivity and specificity.

Renal units with abnormal upper tract cytology were 3 times more likely to develop an upper tract tumor than renal units with normal upper tract cytology. Controlling for previous lower tract TCC and/or CIS, the OR did not change. Thus, the authors infer that abnormal upper tract cytology may be a useful predictor for manifestation of macroscopic upper tract urothelial cancer.

Overall, there were 8 low-grade tumors, 15 moderate to high-grade tumors, and 3 tumors with unknown grade. Abnormal cytology was collected in 11 of the 15 (73.3%) moderate to high-grade and 7 of the 8 (87.5%) low-grade tumors. There appears to be a strong association between abnormal upper tract cytology and upper tract tumor development, regardless

Figure 2. Cumulative Hazard for Development of UT Tumors Over Time With Normal and Abnormal UT Cytology. doi: 10.3834/uij.1944-5784.2009.12.01f2



Log Rank Chi-Square 7.93 (p=0.005)

of grade. In addition, 19 of 26 (73.1%) renal units with upper tract tumors had previous lower tract TCC and/or CIS. It is difficult to draw conclusions from the data given the few patients with a tumor, but it does not limit the risk calculation and time span analyses. The literature shows that the relative risk for upper tract tumors with a previous history of lower tract urothelial carcinoma is 43.2% and 22.2% for Caucasian men and women, respectively, measured at 10 years and based on the SEER database [13].

If a patient is prone to develop upper tract urothelial carcinoma after having abnormal upper tract cytology, when is it likely to be found?

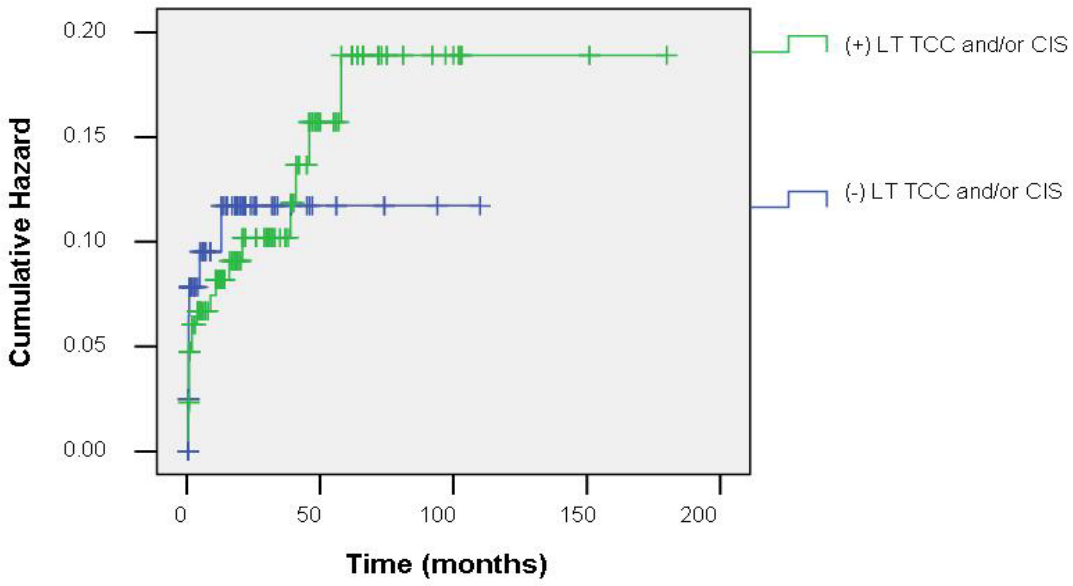
The cohort of 366 renal units was followed for an average of just over 3 years, with a widely variable range. The majority of patients did not develop a tumor within this time period. However, 26 renal units were found to have tumors within 6 years from initial cytology acquisition.

Twenty-two of 26 (84.6%) renal units had upper tract tumors at the time the cytology was collected, which is expected given the indications for upper tract cytology collection. No additional renal units with normal upper tract cytology developed a tumor during the follow-up period. On the contrary, 4 additional renal units with abnormal upper tract cytology developed a tumor over 6 years. Again, this time span highlights the potential ability of upper tract cytology to predict tumor development and illustrates the need for longer observation periods in renal units with abnormal findings.

The Kaplan-Meier hazard curves illustrate the same principle. No renal unit developed a tumor after an initial finding of normal UT cytology, while tumors continued to develop for up to 6 years in those with abnormal UT cytology. Thus abnormal cytology may also be viewed as an incubation period, or anticipatory positive, for certain cells with genetic changes to manifest macroscopic evidence of disease. It then follows that given an initial workup that fails to find evidence of disease, abnormal upper tract cytology may foresee the future development of an upper tract tumor.

Because this is a retrospective study, follow-up was not all equal. Thus, this is the minimum incidence of tumor development over this follow-up period and even more tumors may be expected to develop in subsequent years. It still remains unclear whether more tumors will develop over time because of an age-related phenomenon, prolonged carcinogenic exposure to tobacco, or genetic changes within the urothelium which manifest as macroscopic evidence of disease.

Figure 3. Cumulative Hazard for Development of UT Tumors Over Time With or Without a Previous History of Lower Tract TCC and/or CIS. doi: 10.3834/uij.1944-5784.2009.12.01f2



Log Rank Chi-Square 0.069 (p=0.79)

If a patient is likely to develop upper tract urothelial carcinoma after having abnormal upper tract cytology, how should the patient be followed?

Careful follow-up is necessary for early detection and treatment of disease which may alter the probability of developing advanced local disease, metastatic disease, and death. Future studies are needed to validate the hypothesis that earlier detection and treatment have an impact on these commonly investigated oncologic endpoints. Despite the unknown influence of surveillance on outcome, the present authors suggest that the minimal follow-up of patients with abnormal upper tract cytology should be 6 years. There are certainly a number of patients who may develop a tumor later, but this number is unknown at present time and the maximum length of necessary follow-up is still uncertain.

In the future, researchers need to identify the method of follow-up (eg, imaging, cytology, or direct vision with ureteropyeloscopy) in addition to the frequency of follow-up for these patients. Given the fairly even distribution for the time span of tumor development in the present cohort, the authors suggest that patients do not need more frequent evaluations during any particular time interval over the follow-up period. Nevertheless, further studies are needed in order to determine a reasonable, safe, and economical strategy to monitor at-risk patients for urothelial tumor development.

Limitations

The authors have several concerns that arose during this study. First, it may be premature to propose a particular practice pattern for follow-up based on a small number of patients with upper tract tumors. This disease is not very common, and thus it is difficult to study retrospectively. The authors amassed a fair number of patients with adequate follow-up in the present cohort of patients. However, external validation may be necessary to confirm the generalizability of the results. Second, there is a lack of central review leading to a significant interobserver variability in classifying upper tract cytology and tumors between each cytopathologist and among institutions.

Future Studies

Fluorescence in-situ hybridization (FISH), a cytogenetic-based technology enabling the analysis of chromosomal abnormalities in multiple cells, has been utilized to increase sensitivity for urothelial tumor detection in the lower tract. More recently, it has been used in the detection of upper tract TCC but was

found to have a poor sensitivity (52%), particularly with low-grade tumors [14]. The present authors are considering use of this technology to examine their patients during future studies.

Another potential future study may be a prospective evaluation of all patients demonstrating abnormal upper tract cytology with ureteropyeloscopy and systematic biopsies of the upper tract, regardless of findings. Earlier detection of cytologic or pathologic changes may be better predictors of the progression of macroscopic disease. A final study, currently in planning, would evaluate repeated upper tract cytology studies and whether they persist as either normal or abnormal or convert to the opposite finding. In particular, are there any factors associated with the persistence of or conversion to an abnormal cytology, and is either of these groups of patients more likely to develop tumors?

CONCLUSIONS

Upper tract cytology has a poor sensitivity for tumors of the upper urinary tract. Patients with abnormal upper tract cytology are 3 times more likely to develop TCC than patients with normal upper tract cytology and should be carefully monitored for at least 6 years. However, the exact method and frequency of monitoring remains undetermined.

Conflict of Interest: None declared

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