Upper Tract Imaging Surveillance is not Effective in Diagnosing Upper Tract Recurrence in Patients Followed for Nonmuscle Invasive Bladder Cancer

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Purpose: We evaluated the usefulness of routine upper tract imaging in patients followed for nonmuscle invasive bladder cancer.

Materials and Methods: A retrospective review of patients treated for nonmuscle invasive bladder cancer between 2000 and 2006 was conducted. Kaplan-Meier curves were calculated to determine upper tract urothelial carcinoma-free probability for stage Ta and T1 disease. Bladder cancer stage was included as a time dependent covariate. Descriptive statistics were used to report rates of imaging studies used and the efficacy in diagnosing upper tract urothelial carcinoma.

Results: Of 935 patients treated and followed for nonmuscle invasive bladder cancer 51 were diagnosed with upper tract urothelial carcinoma. Median followup was 5.5 years. The 5-year upper tract urothelial carcinoma-free probability among patients with Ta and T1 disease was 98% and 93%, respectively. The 10-year upper tract urothelial carcinoma-free probability among patients with Ta and T1 disease was 94% and 88%, respectively. Only 15 (29%) patients were diagnosed on routine imaging while the others were diagnosed after symptoms developed. Overall 3,074 routine imaging scans were conducted for an overall efficacy of 0.49%.

Conclusions: Upper tract recurrence is a lifelong risk in patients with bladder cancer, but most cases will be missed on routine upper tract imaging. The majority of upper tract urothelial carcinoma can be diagnosed using a combination of thorough history taking, physical examination, urine cytology and sonography, indicating that routine surveillance imaging may not be the most efficient way to detect upper tract recurrence.

Key Words: carcinoma, transitional cell; urinary bladder neoplasms; diagnostic imaging; watchful waiting
bladder cancer, while routine upper tract imaging is not recommended for patients with low-risk bladder cancer.

Upper urinary tract imaging with CT typically uses contrast enhancement for the opacification of urine. This mode of imaging has the advantage of identifying small lesions with good anatomical characterization, but also involves the hazards of contrast medium and radiation exposure. Contrast medium exposes the patient to possible allergic reactions and contrast induced nephropathy, which is the third most common cause of hospital acquired renal injury. Radiation exposure has the potential hazard of secondary malignancies and it has been estimated that 1.5% to 2.0% of all cancers in the United States may be attributable to radiation from CT. Based on studies extrapolating data accumulated after the Hiroshima and Nagasaki bombs, it has been estimated that exposure to a radiation dose of 10 mSv increases the risk of cancer related death by 0.05%. CT urography exposes the patient to an average dose of 15 mSv but techniques to reduce this exposure have been explored.

To date to our knowledge there are no data to show that obtaining upper tract imaging with CT at routine intervals in the setting of normal cytology and a lack of clinical signs or symptoms lead to an earlier diagnosis of UTUC. We hypothesized that most UTUC is diagnosed after symptoms develop and is missed on routine imaging. Thus, in this study we assess the need for routine upper tract imaging in asymptomatic patients followed for NMIBC.

PATIENTS AND METHODS

After obtaining institutional review board approval we performed a retrospective review of our institutional database to identify patients treated at MSKCC for papillary NMIBC between 2000 and 2006. Data regarding bladder tumor histology and imaging studies were collected from the first diagnosis to the last known followup. The reports of imaging studies were reviewed and included in analysis if they were performed for upper tract surveillance, defined as imaging done at routine surveillance and not for signs or symptoms suggestive of UTUC. Imaging studies performed for other indications related to bladder cancer (ie assessment of postoperative complications, assessment of response to chemotherapy etc) or for indications not related to bladder cancer (ie other malignancies) were not included. Imaging studies were performed at the discretion of the treating physician. Data on symptoms that led to UTUC diagnosis, mode of diagnosis, treatment modality and UTUC histology were also collected.

Patients were excluded from analysis if they had concomitant UTUC at the first bladder tumor diagnosis or if they presented with UTUC before bladder tumor developed. While it is true these patients have a contralateral upper tract system in which UTUC can develop, the risk of contralateral UTUC in this group may be different than that of patients with NMIBC and no previous diagnosis of UTUC. Thus, these patients were excluded from study.

Kaplan-Meier curves were calculated to describe the UTUC-free probability in patients with stage Ta and T1 bladder cancer. Stage was included as a time dependent covariate. Followup time was calculated from the time of diagnosis of the first bladder tumor. We considered using competing risk analyses with death from other causes as the competing event. The results were similar to the Kaplan-Meier method in that patients who died of other causes were censored at the time of death. For simplicity we report Kaplan-Meier estimates. We re-ran the analysis censoring patients at cystectomy (241 patients underwent cystectomy) for sensitivity analysis. Descriptive statistics were used to report on rates of imaging studies. Statistical analyses were conducted using Stata® 12.0.

RESULTS

A total of 935 patients with no previous diagnosis of UTUC were referred to our institution for the treatment of NMIBC during the study period. Median patient age was 66 years (IQR 57, 74). The main patient characteristics are presented in the table. Of the 935 patients UTUC developed in 51. The median followup in patients without a diagnosis of UTUC was 5.5 years. Figure 1 shows the Kaplan-Meier estimates for UTUC-free probability stratified by stage. The 5-year UTUC-free probability among patients with Ta disease was 98% (95% CI 95, 99) and 93% (95% CI 90, 95) among patients with T1 disease. The 10-year UTUC-free probability

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>No. (%)</th>
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<tbody>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>873 (83)</td>
</tr>
<tr>
<td>Black</td>
<td>24 (3)</td>
</tr>
<tr>
<td>Asian</td>
<td>23 (2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>15 (2)</td>
</tr>
<tr>
<td><strong>Primary bladder tumor stage:</strong></td>
<td></td>
</tr>
<tr>
<td>Ta</td>
<td>481 (51)</td>
</tr>
<tr>
<td>T1</td>
<td>454 (49)</td>
</tr>
<tr>
<td><strong>Highest bladder tumor stage during followup:</strong></td>
<td></td>
</tr>
<tr>
<td>Ta</td>
<td>416 (44)</td>
</tr>
<tr>
<td>T1</td>
<td>438 (47)</td>
</tr>
<tr>
<td>Muscle invasive</td>
<td>81 (9)</td>
</tr>
<tr>
<td><strong>Bladder carcinoma in situ:</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>580 (62)</td>
</tr>
<tr>
<td>Yes</td>
<td>355 (38)</td>
</tr>
<tr>
<td><strong>Highest bladder tumor grade during followup:</strong></td>
<td></td>
</tr>
<tr>
<td>Low grade</td>
<td>247 (26)</td>
</tr>
<tr>
<td>High grade</td>
<td>688 (74)</td>
</tr>
<tr>
<td><strong>Treatment:</strong></td>
<td></td>
</tr>
<tr>
<td>Transurethral bladder tumor resection ± intravesical therapy</td>
<td>682 (73)</td>
</tr>
<tr>
<td>Cystectomy</td>
<td>226 (24)</td>
</tr>
<tr>
<td>Partial cystectomy</td>
<td>13 (1)</td>
</tr>
<tr>
<td>Chemoradiation</td>
<td>14 (1)</td>
</tr>
</tbody>
</table>
was 94% (95% CI 90, 97) among patients with Ta disease and 88% (95% CI 82, 92) among those with T1 disease. The 5 and 10-year survival probabilities for patients with Ta disease were identical between the main and sensitivity analyses, censoring patients at cystectomy. The 5 and 10-year survival probabilities were lower among patients with T1 disease after censoring at cystectomy. However, the confidence intervals were wide.

UTUC developed in 29 patients in this cohort within 5 years of the first episode of NMIBC. UTUC developed in 22 patients 5 years or more after the initial NMIBC episode with 3 instances more than 20 years after the first episode of NMIBC.

UTUC was diagnosed in 16 patients with Ta bladder cancer, including 10 (63%) after symptoms developed, 4 (25%) on routine imaging and 2 (12%) unknown. Of 33 patients with T1 disease diagnosed with UTUC, 20 (61%) were diagnosed after symptoms developed, 9 (27%) were diagnosed on routine imaging and in 4 (12%) a diagnosis could not be determined. The presence of bladder CIS did not affect the rate of diagnosis of UTUC on routine imaging. Twenty-five patients diagnosed with UTUC had bladder CIS. Of 15 patients diagnosed with UTUC on routine imaging 8 had CIS and 7 did not.

High grade UTUC was diagnosed in 12 of 15 (80%) cases diagnosed on routine imaging and in 26 of 36 (72%) cases missed on routine imaging. Noninvasive UTUC (Ta or CIS) was diagnosed in 10 of 15 (67%) cases diagnosed on routine imaging and 15 of 36 (42%) cases missed on routine imaging. Of 15 patients diagnosed on routine imaging 3 (20%) had invasive UTUC, while a stage was not available in 2 patients who had biopsy proven high grade UTUC but were not treated surgically at MSKCC.

Of the 36 cases missed on routine imaging 14 (39%) had invasive UTUC diagnosed. Stage was not available for 5 patients and 2 had pathological stage T0 disease at resection after biopsy proven high grade UTUC.

Of 15 patients with UTUC diagnosed on routine imaging 4 (27%) had hydronephrosis and, thus, sonography would have indicated the need for further evaluation. Of the 11 patients diagnosed on routine imaging without hydronephrosis, 8 had positive urine cytology at the time of diagnosis. The remaining 3 patients diagnosed on routine imaging without hydronephrosis and negative cytology had noninvasive disease of the distal ureter (2 with high grade disease).

The symptoms and signs that led to a diagnosis of UTUC in cases missed on routine imaging were hematuria, cystoscopic findings (recurrent tumors around a ureteral orifice), flank pain, new onset renal failure, sonographic hydronephrosis, unexplained abnormal cytology, recurrent urinary tract infections and an incidental finding at cystectomy.

As there are different surveillance guidelines for stage Ta, low vs high grade, we also explored differences in UTUC-free probability between patients with low and high grade Ta disease. Our subgroup analyses of patients with primary stage Ta disease showed that there was no significant difference in UTUC-free probability between the 2 groups (log rank p = 0.6, fig. 2).

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of bladder cancer, 3% underwent 11 to 15 CT studies and 1% underwent 16 to 20 CT studies. By stage the mean number of imaging studies per patient was 2 and 3 for Ta and T1, respectively. Patients with CIS of the bladder underwent considerably more imaging studies compared to those without CIS (mean 5 vs 2.6 studies per patient, respectively), reflecting the higher risk of UTUC in these patients. Overall 3,074 routine CT studies were conducted, of which UTUC was diagnosed in 15 for an efficacy of 0.49%.

DISCUSSION

Patients with bladder cancer are at increased risk for UTUC. Although the risk of UTUC is low, it is constant during a long followup with patients in the current cohort having recurrence as far out as 27 years from the initial diagnosis. The longitudinal risk of UTUC after cystectomy for bladder cancer has been shown to be steady over time when competing risks and landmark analysis methodology was used to evaluate the incidence of upper tract recurrence after radical cystectomy. Another group from our institution used the SEER (Surveillance, Epidemiology and End Results) database to show the incidence of UTUC was stable among patients with bladder cancer.

Because of the long-term risk of UTUC, patients followed for bladder cancer are subjected to lifelong upper tract surveillance using imaging modalities such as IVP and CT/magnetic resonance urography. This is reflected in all major urological guidelines that recommend periodic routine upper tract imaging, especially in high risk patients. In contrast, other authors have argued against upper tract surveillance in light of the low risk of UTUC and the significant number of cases missed on routine surveillance imaging. Holmång et al reported on a low incidence of UTUC (16 of 680 patients followed for bladder cancer), with half of these patients not diagnosed despite routine imaging with IVP during the 10 months before the diagnosis of UTUC. Another report also showed a low incidence of UTUC (6 of 174 patients followed for bladder cancer) detected with IVP. All the patients in whom UTUC developed in this series had recurrent bladder tumors. Thus, the authors concluded that upper tract surveillance can be abandoned in patients without a recurrence at 24 months. Millán-Rodríguez et al described the rate of UTUC detected by biannual IVP in a cohort of 1,529 patients followed for NMIBC, stratified by risk. They concluded that low risk patients do not need upper tract imaging surveillance while high risk patients might benefit from more stringent upper tract surveillance. Because the upper tract imaging modality used in these 3 studies was IVP, it can be argued that current upper tract imaging with CT urography is more sensitive and should have a lower rate of missed UTUC.

This report is one of the largest studies on UTUC in patients with bladder cancer, with CT constituting more than 90% of imaging studies included. In this study we have shown that UTUC is uncommon in patients with NMIBC, especially in those with low stage disease. Interestingly, patients with low stage bladder cancer (Ta disease) had a low incidence of UTUC regardless of tumor grade.

The low incidence of UTUC, the high percentage of tumors missed on routine imaging, and the fact that half of the patients diagnosed on routine imaging had low grade and low stage disease all support the idea that routine upper tract imaging in asymptomatic patients followed for NMIBC may not be efficacious. The upper tracts of patients with symptoms suggestive of upper tract obstruction, unexplained hematuria or abnormal cytology should be explored with appropriate imaging or with upper tract endoscopy. Based on the findings in our cohort an alternative to routine cross-sectional imaging may be history and physical examination, urine cytology and sonographic upper tract surveillance, which would have identified all but 3 patients (6%) in our cohort, thus decreasing the risk of radiation and contrast media exposure for the majority of the patients.

Because the investigation of hematuria includes upper tract imaging and because 6% of our cohort presented with an upper tract tumor before or at the first episode of bladder cancer, it is prudent to image the upper tract of all patients with NMIBC at least once during the initial evaluation. In addition, imaging may provide information concerning local and distant extent of disease.

We appreciate the shortcomings of our study. The retrospective nature, select patient group and small number of upper tract recurrences are the major limitations. The retrospective nature of this study likely resulted in the underestimation of the number of imaging studies and the percentage of UTUC that developed during followup. Because most patients were referred to our institution after a period of surveillance elsewhere, the number of imaging studies performed before the referral is probably higher than that recorded in our database. It is also possible that some of the patients were diagnosed with and treated for UTUC elsewhere after completing treatment at MSKCC and, thus, were not captured in this report.

Our cohort was composed of patients with high risk NMIBC as can be appreciated by the relatively low percentage of Ta disease (44%) compared to that reported in epidemiological studies (approximately
70% of all patients with NMIBC), and by the complexity of the patients seen by the high percentage treated with cystectomy (26%) after bladder preserving therapy failed or because of the disease extent and inability to control the disease with transurethral resection and intravesical therapy. Although our cohort does not represent the general population of patients with NMIBC, we believe it does not preclude using our results to guide upper tract surveillance in lower risk populations.

The main advantages of our study are the large cohort and the long followup. With a median followup of 5.5 years, it is highly reasonable that our results closely represent the true rate of UTUC among patients with NMIBC and the number of imaging studies patients undergo during this period.

**CONCLUSIONS**

While upper tract recurrence remains a lifelong risk for patients with bladder cancer, only a minority will be diagnosed on routine surveillance CT urography. The majority of UTUC can be diagnosed with a surveillance strategy including thorough history, physical examination, urine cytology, cystoscopy and renal sonography. We believe our findings are sufficient to support a prospective study to validate these findings as an alternative to current surveillance imaging guidelines.

**REFERENCES**


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