Radiographic predictors of muscle-invasive upper tract urothelial cancer: A Canadian cohort

David Chung[1]; Ryan Ramjiawan[1]; Dhiraj S. Bal[2]; Robert Wightman[3]; Jasmir G. Nayak[1,4]; Jeffery W. Saranchuk[1], Rahul K. Bansal[5], Ardalan E. Ahmad[1]

[1]Section of Urology, Department of Surgery, University of Manitoba, Winnipeg, MB, Canada; [2]Max Rady College of Medicine, University of Manitoba, Winnipeg, MB, Canada; [3]Department of Pathology, University of Manitoba, Winnipeg, MB, Canada; [4]Men's Health Clinic Manitoba, Winnipeg, MB, Canada; [5]Division of Urology, Department of Surgery, McMaster University, Hamilton, ON, Canada

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Corresponding Author: Dr. David Chung, Section of Urology, Department of Surgery, University of Manitoba, Winnipeg, MB, Canada; chungt3@myumanitoba.ca

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ABSTRACT

KEY MESSAGES

- At multiple institutions in Manitoba, preoperative radiologic factors, such as severity of hydronephrosis, and location of tumor were not significant predictors of adverse pathologic outcomes.
- Presence of hydronephrosis was predictive of T2 disease or higher on univariate analysis; however, was not found to be a significant predictor on our multivariate analysis.
- Overall, CT urogram was able to accurately predict location of tumor in 74.6% of patients; however poor performance can be seen with proximal/renal pelvis tumors and carcinoma in situ.

Introduction: Accurate diagnostic staging of upper tract urothelial cancer (UTUC) is challenging. Endoscopic staging is limited by its ability to provide adequate sampling of deeper layers of the ureter and renal pelvis. Further ability to accurately predict invasive disease would aid in better selecting the appropriate treatment for patients. We aimed to analyze the ability of preoperative cross-sectional radiologic findings to predict pathologic outcomes, including tumor grade, muscle-invasive disease, and presence of lymphovascular invasion (LVI).
Methods: All patients diagnosed with localized UTUC (cN0M0) who underwent nephroureterectomy between February 2012 and December 2018 in Manitoba, Canada, were identified. Preoperative radiologic characteristics, including the presence and severity of

hydronephrosis, as well as tumor location were recorded. Patients' and pathologic characteristics were also recorded. Logistic regression analysis was used to assess the association between radiologic variables and pathologic outcomes at radical surgery.

Results: A total of 112 pathology reports of patients with UTUC were obtained. The median age was 70 years (range 50–87), and 58.8% of patients were men. On univariate analysis, ureteric location on computed tomography (odds ratio [OR] 2.240, 95% confidence interval [CU] 1.049–4.783, p=0.037) and presence of hydronephrosis (OR 2.455, 95% CI 1.094–5.506, p=0.0029) were each independently associated with locally invasive disease (≥pT2). No radiologic variables were found to be a predictor of adverse pathology on multivariable analysis. Only the presence of hydronephrosis was associated with high-grade disease on univariate analysis (OR 2.533, 95% CI 1.083–5.931, p=0.032).

Conclusions: Our findings suggest a limited role for cross-sectional imaging in predicting the presence of high-grade disease, LVI, or locally advanced disease in UTUC.

INTRODUCTION

Upper tract urothelial cancer (UTUC) refers to malignant alterations in the urothelial cells forming the inner lining of the urinary tract ranging from the renal calyces, pelvis, or along the ureter to the ureteral orifice.[1] While UTUC is relatively uncommon and only accounts for 5% of all urothelial cancers, it is known for its invasive and potentially aggressive nature.[1,2] Approximately two-thirds of UTUC cases are invasive at the time of diagnosis. This compares to 15-25% invasiveness observed in muscle-invasive bladder cancer (MIBC).[3] The ability to distinguish invasive UTUC is of great prognostic significance as invasive disease is associated with worse outcomes, with 5-year cancer-specific survival rates of 86% for non-muscle invasive UTUC and 70-77% for muscle-invasive disease[4,5].

The current diagnostic workup for UTUC involves a combination of cross-sectional imaging (CT urogram [CTU] is preferred or MR urogram), diagnostic ureteroscopy (URS) and possible biopsy, and urine cytology. However, there are challenges associated with the use of URS and biopsy, including limitations in obtaining a conclusive biopsy to accurately determine disease stage and the potential for increased risk of intravesical recurrence.[6,7] Previous studies have indicated that certain radiologic variables, such as preoperative hydronephrosis and ureteral location, may serve as predictors of advanced pathological stage.[8-12] The ability to accurately determine disease stage has major clinical implications, including optimal patient selection for minimally invasive treatments and choosing patients who may benefit from neoadjuvant chemotherapy (NAC), which has shown promising results in phase II trials and systematic reviews.[13,14] Additionally, the ability to identify patients with higher stage disease (≥ cT2)could help guide in selecting patients who should be considered for lymph node dissection.[15]

Given the opportunity to enhance the selection of the most appropriate treatment modalities for UTUC and improve patient outcomes, it would be important to determine whether preoperative radiologic characteristics are associated with surgical pathological outcomes. The objective of this study was to evaluate the predictive ability of preoperative radiological findings for pathologic outcomes, including tumour grade, invasive disease (≥pT2), and the presence of lymphovascular invasion.

METHODS

We conducted a retrospective chart review utilizing the Manitoba pathology database. This database stores all UTUC specimens for patients who underwent surgery in the Province of Manitoba, Canada. Patients from four institutions (two tertiary care and two community-based hospitals) undergoing radical surgery with nephroureterectomy for localized UTUC (cN0M0) between February 1, 2012, and December 31, 2018, were included. Institutional review board approval was received (HS22554).

Patients and disease characteristics, including pathologic tumour grade, TNM stage, multifocality, presence of lymphovascular invasion and preoperative cross-sectional imaging radiologic characteristics, were collected. Clinical nodal stage was based off obtained cross-sectional imaging radiologic report. Specifically, the radiologic characteristics included were presence of hydronephrosis, severity of hydronephrosis, tumour location, and presence of lymphadenopathy. Characteristics were collected through available radiologic reports. Patients were excluded if missing pathology data and if radiologic reports did not comment on hydronephrosis, degree of hydronephrosis, and location of tumour on imaging. The degree of hydronephrosis was categorized into mild, moderate, or severe based on the radiology report. As for the location of the tumour on imaging, these were categorized as ureteric location and/or renal pelvis/caliceal.

Descriptive statistics were used for baseline characteristics. Univariate and multivariable logistic regression analysis was performed using SPSS (Version 29.0.2) to assess the predictive value of the following preoperative radiographic findings (hydronephrosis, severity of hydronephrosis, tumour location on imaging). Two-sided statistical significance was set at p=0.05.

RESULTS

One hundred and twenty-two patients were diagnosed with localized UTUC (cN0M0) during the study period. 112 were included in the study with 10 patients being excluded for either missing radiology data and/or reports that did not comment on degree of hydronephrosis or the location of the possible tumour (Figure 1).

Baseline characteristics, including patient demographics, tumour characteristics and preoperative radiographic findings, are detailed in Table 1 and 2. The median age was 70 years (50-87), and 58.8% of patients were men. For tumour characteristics on the final pathologic specimen, 71.1% (n=81) were high-grade tumours, and 22.8% (n=26) showed the presence of

LVI. 52 patients (45.6%) had pathologic stage ≥T2 on final pathology. For lymph node (LN) status on final pathologic specimen, 72% (n=81) were Nx, 19% (n=21) were N0, 3% (n=3) were N1, and finally 6% (n=7) were N2. Regarding radiologic characteristics, 63.2% (n=72) had evidence of hydronephrosis on preoperative diagnostic imaging. 57 patients (50%) had ureteric tumours and 48.2% (n=55) had renal pelvis or caliceal tumours. CT scan was able to accurately assign the location of tumour on final pathology 74.6% of the time. As for LN status on pre-operative imaging, 4 patients had positive nodes detected on CT scan, all of which who had N1 or N2 disease on final pathology. 4 patients were identified to have sub-centimeter nodes, 2 of which had node positive disease on final pathology. Finally, 104 patients did not have significant lymphadenopathy on pre-operative imaging, however 4 of these patients went on to have node positive disease on final pathology.

On logistic regression analyses for predictors of pathologic stage of pT2 or higher, ureteric location on CT (OR 2.240 (p=0.037; CI 1.049-4.783)) and presence of hydronephrosis (2.455 (p=0.029; CI 1.094-5.506)) were found to be statistically significant predictors of ≥ pT2 disease on univariate analysis as seen in Table 3. On multivariable analysis, none of the radiologic variables were found to be significantly associated with ≥ pT2 disease.

For predictors of high-grade disease on univariate analysis, only the presence of hydronephrosis was found to be a significant predictor (OR 2.533 (p=0.032; 1.083-5.931)), while presence of moderate/severe hydronephrosis (OR 2.357 (p=0.077; 0.91-6.104)) and ureteric location on CT (OR 1.979 (p=0.113; 0.850-4.608)) did not reach significance. None of the above variables reached significance on multivariable analysis (Table 4).

Finally, for predictors of lymphovascular invasion, all three radiographic variables: presence of hydronephrosis, presence of moderate/severe hydronephrosis, and ureteric location on CT, were not significant predictors of LVI on univariate and multivariable analysis (Table 5).

DISCUSSION

There has been an increasing interest in preoperative predictors of advanced disease in UTUC. The ability to accurately determine disease stage has major clinical implications, including optimal patient selection for minimally invasive treatments and choosing patients who may benefit from neoadjuvant chemotherapy (NAC), which has shown promising results in phase II trials and systematic reviews.[13,14] Despite advancements in imaging technologies, modern cross-sectional imaging is limited in its ability to accurately predict the degree of invasion for UTUC. Recent studies have investigated the utility of preoperative radiographic characteristics to predict invasive UTUC. The objective of this study was to evaluate the predictive ability of preoperative radiological findings for pathologic outcomes, including tumour grade, muscle-invasive disease, and the presence of lymphovascular invasion. We found that the presence of hydronephrosis on preoperative imaging and ureteric tumour location are associated with pathologic stage ≥ pT2 on univariate regression analysis but not on multivariable analysis. Although cross-sectional imaging was also able to correctly assign the tumour location on final pathology 74% of the

time, ureteroscopic examination of the proximal collecting system should strongly be considered in patients who are deemed suitable candidates for segmental ureterectomy.

In our multi-institutional retrospective cohort study, hydronephrosis was found to be an independent predictor for ≥ pT2 disease and high-grade disease on final pathology. However, the degree of hydronephrosis was not a significant predictor of worse pathologic outcomes. On multivariable analysis, hydronephrosis was not associated with worse pathologic outcomes. Presence of hydronephrosis on preoperative imaging has been proposed as a predictor of advanced pathologic stage. The prevailing hypotheses are that more advanced tumours lead to progressive luminal obstruction and subsequent hydronephrosis. This relationship has been demonstrated in multiple studies.[1,2] Messer et al. showed that hydronephrosis was associated with ≥ pT2 disease, high-grade, and non-organ confined disease on regression analysis adjusting for tumour location.[3] This was similar to what was seen in our study; however, this relationship was not seen on multivariable analysis once adjusting for the tumour location. There have been conflicting studies in terms of using preoperative hydronephrosis as a prognostic predictor.[4,5,18] A recent systematic review and meta-analysis was published by Ye et al. to provide further understanding of this relationship.[6] Of the 7,542 patients included, they found that preoperative hydronephrosis was significantly associated with worse pathologic outcomes as well as worse oncological outcomes such as overall survival, cancer-specific survival, and disease-free survival.

In terms of the relationship between hydronephrosis and lymphovascular invasion, it has been postulated that the increased intraluminal pressure due to hydronephrosis may cause counterflow, promoting tumour seeding.[7] LVI is an important pathologic variable to consider as it has been associated with a worse prognosis. In our cohort, the presence of hydronephrosis, the severity of hydronephrosis and ureteric tumour location on preoperative imaging were not independent predictors of lymphovascular invasion on multivariable analysis. Previously it has been demonstrated that hydronephrosis was associated with lymphovascular invasion. However, there are some key differences in these respective studies. Ito et al. did not include tumours of caliceal location while having objective measures of hydronephrosis seen on radiology reports.[2] Other studies demonstrating an association between hydronephrosis and LVI/lymph node involvement were only among patients with high-grade disease seen on the final pathology specimen, which we elected not to include in our analysis as this information would not be available during preoperative risk stratification.[7,19] An argument can be made that data can be extrapolated to specimens obtained endoscopically, however, there can be significant discordance between biopsy specimen tumour grade and final pathology, especially in larger upper tract urothelial tumours.[18]

In our study, ureteric location was found to be a predictor of ≥ pT2 disease on univariate analysis only. There is increasing evidence that patients with ureteral tumours compared to renal pelvic tumours demonstrate a worse prognosis and outcome. Multiple studies have demonstrated that ureteric location of the tumour on the final pathology specimen is associated with more

advanced disease and higher incidence of lymphovascular invasion.[8-11] The prevailing hypothesis is that the thinner muscularis layer of the ureter makes this location more prone to the development of more invasive disease as well as lymphovascular spread. Interestingly, Lwin et al. and Williams et al. found that tumour location does not appear to have any influence on long-term oncologic outcomes.[12,13] Nonetheless, the European Association of Urology UTUC guidelines currently do not recommend using the primary ureteric location of a tumour to stratify patients into the high-risk category. Our study was unique in using the location of tumour on preoperative imaging as an independent predictor, as this may be a more clinically meaningful predictor than tumour location on final pathology, which would not be applicable for pre-treatment decision-making. However, ureteric location on CT was only shown to be an independent predictor on univariate analysis but not multivariate analysis.

While the ability to use the location of tumour on preoperative imaging to help risk stratify UTUC patients may be more practical in real-world practice, an important question is how accurately axial imaging can predict location of tumours. In our cohort, preoperative imaging was able to correctly identify the location of the primary tumour on final pathology in 75% of cases. CTU has the highest diagnostic accuracy, with a meta-analysis demonstrating a pooled sensitivity and specificity of 92% and 95%, respectively.[14] The ability of imaging to accurately localize the location of tumour is less understood. A retrospective study of 275 patients by Abouelkheir et al. found that CTU had an overall accuracy of 97%. However, in terms of detecting the location of tumour on final pathology, results were variable with CTU showing the highest accuracy in diagnosing location of renal pelvis and distal ureteric tumours, with poor performance for calyceal and proximal tumours.[15] It is still important to acknowledge that false negatives may be possible with CTU, as there is evidence that small tumours and carcinoma in situ (CIS) may be missed on cross-sectional imaging.[16,17] Further prospective studies would be required to further investigate the ability of CTU in accurately determining the tumour location to see if it could potentially replace the need for ureteroscopy.

Limitations

There are limitations to our study. This was a retrospective study with inherent limitations attributable to its design. Our sample size was also limited, given the rare incidence of UTUC in the population, therefore our multivariate analysis was likely underpowered. Additionally, for the presence and severity of hydronephrosis, we relied on radiologic reports as no central review by a radiologist or urologist was conducted. Cross-sectional imaging was reported by various radiologists which may introduce interobserver variability affecting variables such as degree of hydronephrosis and nodal status, limiting our results. Furthermore, we acknowledge multifocality is an important prognosticator, however given the limitation inherent to relying on radiology reports, this information was not able to be reliably captured. Given the variability and inconsistent reporting, certain radiographic findings, such as periureteral invasion suggestive of invasive disease and tumor size were not included in this study. There is also the possibility of selection bias as only candidates for surgical intervention were included and patients with

missing preoperative radiographic findings were not included. We were also unable to assess other variables that may have had a role in the pathological outcome, including delay from diagnosis to surgery, biopsy grade, tumour size on imaging, tumour multifocality, and other clinical factors.

CONCLUSIONS

At multiple institutions in Manitoba, preoperative radiologic factors such as hydronephrosis and the location of tumour were not significant predictors of T2 disease or higher. However, further larger scale studies are required to elucidate the role of preoperative radiologic findings in predicting pathologic outcomes.

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FIGURES AND TABLES

Figure 1. Flow diagram depicting included and excluded patients.

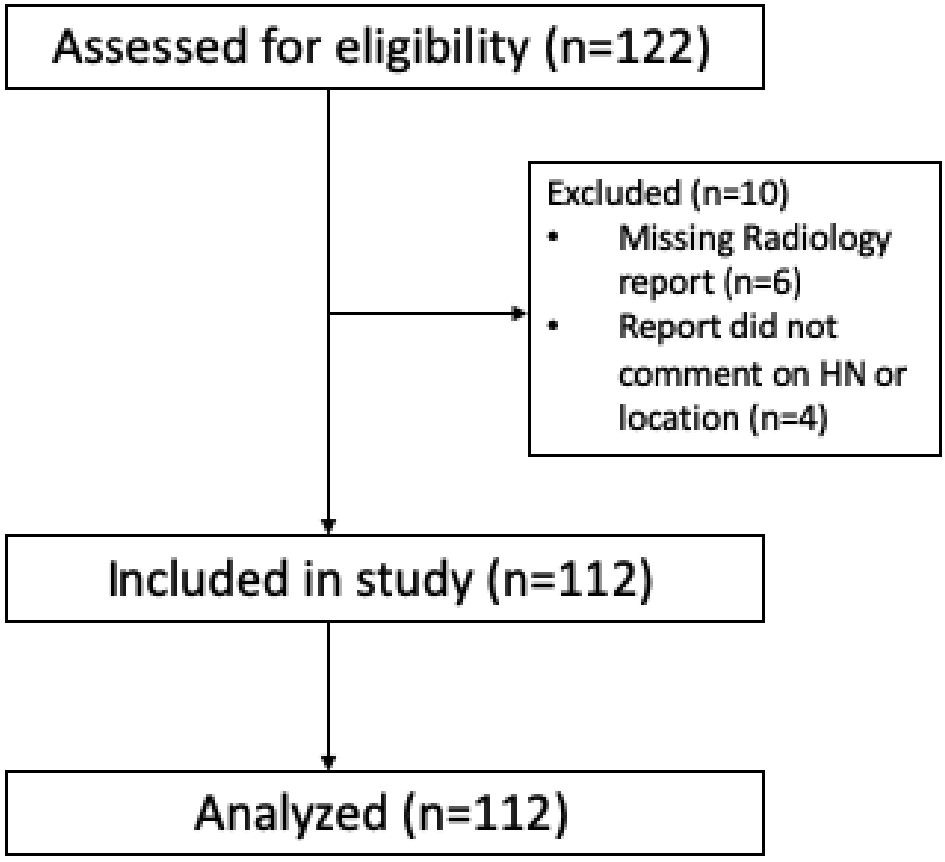

Table 1. Patient demographics	
Variable	**Value**
Total number of patients	112
Median age (years)	70 (range 50–87)
Male gender (%)	67 (58.8%)
Tumor location on CT	
Ureteric location (%)	57 (50)
Renal pelvic or above location (%)	55 (48.2)
Not available (%)	2 (1.8)
CT/pathology congruency of location (%)	85 (74.6%)
Presence of hydronephrosis (%)	72 (63.2)
Presence of moderate/severe hydronephrosis (%)	40 (35.1)
Pathologic grade	
High (%)	81 (71.1)
Low (%)	31 (27.2)
Pathologic node status	
Nx	81 (72%)
N0	21 (19%)
N1	3 (3%)
N2	7 (6%)
Presence of lymphovascular invasion (%)	26 (22.8)
Pathologic stage pT2 or higher (%)	52 (45.6%)

CT: computed tomography.

Table 2. Tumor characteristics on final pathology			
Variable	**Renal pelvic tumors (n=54)**	**Ureteral tumors (n=35)**	**Multifocal tumors (n=22)**
Pathologic stage, number (%)			
Ta	23 (42.6)	10 (28.6)	6 (27.3)
T1	9 (16.7)	4 (11.4)	4 (18.2)
T2	5 (9.3)	6 (17.1)	3 (13.6)
T3	13 (24.1)	14 (40)	6 (27.3)
T4	3 (5.6)	0 (0)	2 (9)
Tis	1 (1.9)	1 (2.9)	6 (27.3))
Grade			
High (%)	35 (64.8)	29 (82.9)	16 (72.7)
Low (%)	19 (35.2)	6 (17.1)	6 (27.3)
Presence of lymphovascular invasion (%)	9 (16.7)	8 (22.9)	8 (36.4)

Table 3. Logistic regression analysis of association of radiologic variables and presence of pT2 or higher disease				
Variable	**Univariate analysis**		**Multivariable analysis**	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**
Presence of hydronephrosis	2.455 (1.094–5.506)	**0.029**	1.770 (0.709–4.414)	0.221
Presence of moderate/severe hydronephrosis	1.250 (0.576–2.173)	0.572	1.880 (0.708–4.997)	0.205
Ureteric location on CT	2.240 (1.049–4.783)	**0.037**	1.831 (0.778–4.310)	0.166

CI: confidence interval; CT: computed tomography; OR: odds ratio.

Table 4. Logistic regression analysis of association of radiologic variables and presence of high-grade tumor				
Variable	**Univariate analysis**		**Multivariable analysis**	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**
Presence of hydronephrosis	2.533 (1.083–5.931)	**0.032**	2.081 (0.863–5.017)	0.103
Presence of moderate/severe hydronephrosis	2.357 (0.91–6.104)	0.077	2.494 (0.923–6.735)	0.071
Ureteric location on CT	1.979 (0.850–4.608)	0.113	2.187 (0.871–5.489)	0.096

CI: confidence interval; CT: computed tomography; OR: odds ratio.

Table 5. Logistic regression analysis of association of radiologic variables and presence of lymphovascular invasion				
	Univariate analysis		**Multivariable analysis**	
Variable	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Presence of hydronephrosis	1.690 (0.641–4.456)	0.289	1.475 (0.543–4.008)	0.446
Presence of moderate/severe hydronephrosis	1.167 (0.471–2.887)	0.739	2.326 (0.713–7.586)	0.713–7.586
Ureteric location on CT	1.167 (0.484–2.811)	0.484–2.811	1.001 (0.404–2.478)	0.998

CI: confidence interval; CT: computed tomography; OR: odds ratio.