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Combining imaging and ureteroscopy variables in a preoperative multivariable model for prediction of muscle-invasive and non-organ confined disease in patients with upper tract urothelial carcinoma

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What's known on the subject? and What does the study add?
Improved patient selection for conservative management, neoadjuvant chemotherapy, and/or extended lymphadenectomy is urgently needed. We developed a highly accurate preoperative model to predict muscle-invasive and non-organ-confined upper tract urothelial carcinoma based on standard imaging and ureteroscopy features.

OBJECTIVE

- To create a preoperative multivariable model to identify patients at risk of muscle-invasive (pT2+) upper tract urothelial carcinoma (UTUC) and/or non-organ confined (pT3+ or N+) UTUC (NOC-UTUC) who potentially could benefit from radical nephroureterectomy (RNU), neoadjuvant chemotherapy and/or an extended lymph node dissection.

PATIENTS AND METHODS

- We retrospectively analysed data from 324 consecutive patients treated with RNU between 1995 and 2008 at a tertiary cancer centre.
- Patients with muscle-invasive bladder cancer were excluded, resulting in 274 patients for analysis.
- Logistic regression models were used to predict pT2+ and NOC-UTUC. Pre-specified predictors included local invasion (i.e. parenchymal, renal sinus fat, or periureteric) on imaging, hydronephrosis on imaging, high-grade tumours on ureteroscopy, and tumour location on ureteroscopy.
- Predictive accuracy was measured by the area under the curve (AUC).

RESULTS

- The median follow-up for patients without disease recurrence or death was 4.2 years.
- Overall, 49% of the patients had pT2+, and 30% had NOC-UTUC at the time of RNU.
- In the multivariable analysis, only local invasion on imaging and ureteroscopy high grade were significantly associated with pathological stage.
- AUC to predict pT2+ and NOC-UTUC were 0.71 and 0.70, respectively.

CONCLUSIONS

- We designed a preoperative prediction model for pT2+ and NOC-UTUC, based on readily available imaging and ureteroscopic grade.
- Further research is needed to determine whether use of this prediction model to select patients for conservative management vs RNU, neoadjuvant chemotherapy, and/or extended lymphadenectomy will improve patient outcomes.

KEYWORDS

nephroureterectomy, prognosis, renal pelvis, transitional cell carcinoma, urothelial carcinoma

INTRODUCTION

Upper tract urothelial carcinoma (UTUC) is an uncommon disease. Radical nephroureterectomy with excision of the bladder cuff (RNU) is considered the current standard of care for the treatment of nonmetastatic UTUC, especially for muscle-invasive or high-grade disease. Unfortunately, UTUC is a biologically aggressive malignancy with the potential for disease recurrence and cancer-specific

mortality, even after excellent local control [1].

Several postoperative prognostic risk factors have been identified to help in the clinical decision-making for optimal management. The widely accepted ones consist of pathological stage, lymph node (LN) status, tumour grade, and extent of surgery [2–17]. The rationale for postoperative assessment lies in the ability to direct interventions to the patients who are most likely to benefit, e.g. administering adjuvant chemotherapy to patients with high-risk tumours. However, the use of adjuvant chemotherapy regimens is currently hampered by the lack of randomized trials showing evidence of efficacy [18,19] and the difficulty in using cisplatin-based chemotherapy due to postoperative renal insufficiency [20,21].

A better alternative is to identify patients with muscle-invasive (pT2+) or non-organ-confined UTUC (NOC-UTUC) Before RNU. Using this approach, the patients best suited for RNU vs conservative management (i.e. endoscopic), neoadjuvant chemotherapy vs none, and more extensive lymphadenectomy vs standard or no lymphadenectomy could be selected a priori. An additional advantage of administering chemotherapy in the preoperative setting is that the patient has better renal function before RNU, thus allowing administration of cisplatin-based therapy. In patients with bladder cancer, neoadjuvant chemotherapy has also been shown to improve survival [22], and it has been postulated that this benefit may be extrapolated to patients with UTUC [19,23]. Investigators have also shown a survival benefit for more extensive lymphadenectomy in patients with UTUC with locally advanced disease [24]. Unfortunately, RNU with or without chemotherapy and/or extended lymphadenectomy may expose patients to increased morbidity. For these reasons, an accurate preoperative prediction of pT2+ and NOC-UTUC is needed to risk stratify and select appropriate patients for these treatments.

Our primary objective was to develop a preoperative multivariable model, combining imaging and ureteroscopic variables to accurately identify patients who are at risk for pT2+ and NOC-UTUC, and who would therefore benefit from RNU, neoadjuvant chemotherapy and/or an extended LN dissection. We hypothesize that the addition of imaging variables to a multivariable model would improve its predictive accuracy.

PATIENTS AND METHODS

After Institutional Review Board approval, we retrospectively reviewed all prospectively collected data of the 324 consecutive patients presenting with UTUC and treated with RNU at Memorial Sloan-Kettering Cancer Center (MSKCC) between 1995 and 2008. We excluded patients who underwent previous or concurrent radical cystectomy (46 patients), had prior contralateral UTUC (four), or had metastatic UTUC before RNU (three). The remaining 274 patients were the subjects of the present analysis.

UTUC was diagnosed by CT of the abdomen and pelvis, MRI, ureteroscopy with or without biopsy, and voided and wash/brush cytology. Hydronephrosis and local invasion on imaging (i.e. renal parenchymal, renal sinus fat, or periureteric tissues) were assessed from radiographic reports of upper tract imaging, including CT and MRI. Only imaging done within 6 weeks of RNU was included for evaluation. Ureteroscopy grade was assessed by biopsy or wash/brush cytology.

RNU was performed by experienced urological oncology surgeons at MSKCC using a standardized approach, including the removal of the kidney with the entire length of the ureter and adjacent segment of the bladder cuff. The hilar and regional LNs adjacent to the ipsilateral great vessels were resected. Extended lymphadenectomy was only performed if locally advanced disease (pT3+ or N+) was suspected.

For pathological evaluation, all surgical specimens were processed according to standard pathological procedures at our institution and were histologically confirmed to be UCs. UTUC was defined as UC located in i) the renal pelvis or calyces or ii) within the ureter. Tumours were staged according to the 2002 American Joint Committee on Cancer/Union Internationale Contre le Cancer TNM classification. Tumour grading was assessed according to the 1998 WHO/International Society of Urological Pathology consensus classification [25]. The location of the tumour was assessed by ureteroscopy and categorized as renal pelvis or ureteric. In the case of multifocal tumours, the index lesion was defined as that with the highest pathological tumour stage and/or grade.

Patients were followed-up every 3 months for the first year after RNU, every 4 months for the second year, every 6 months from the third to the fifth years, and annually thereafter. Follow-up consisted of a history, physical examination, routine blood work and serum chemistry studies, urinary cytology, chest radiography, cystoscopic evaluation of the urinary bladder, and radiographic evaluation of the contralateral upper urinary tract. Since November 2001, CT urograms have formed the standard imaging method for evaluating the abdomen and pelvis for urothelial recurrence at our institution. Elective bone scans, chest CT, and MRI were performed when clinically indicated.

To identify predictors of pathological stage at the time of RNU, we created two separate univariate logistic regression models to predict pT2+ and NOC-UTUC (pT3+ or N+). The pre-specified predictors were local invasion on imaging, hydronephrosis on imaging, high-grade tumours identified on ureteroscopy (herein called ureteroscopy high-grade), and tumour location as determined by ureteroscopy. To determine whether the addition of the two imaging variables to a model based on ureteroscopy variables would improve predictive accuracy, we compared the discrimination from a base model (using only grade and location as predictors) to that of the more complex model (using grade, location, local invasion on imaging, and hydronephrosis). Discrimination was measured by the area-under-the-curve (AUC). Comparisons were tested using the likelihood ratio test.

RESULTS

The median age of patients was 72 years; approximately two-thirds (62%; 171) of the patients were men (Table 1). About half (51%, 139) of the patients had evidence of hydronephrosis on imaging, and 15% (41) had evidence of local invasion on imaging.

In all, 133 patients (49%) had pT2+ at the time of RNU, and 82 (30%) had NOC-UTUC. In univariate analysis, local invasion on imaging ($P < 0.001$), hydronephrosis ($P = 0.011$), and ureteroscopy high-grade ($P = 0.023$) were all significantly associated with increased risk of pT2+ (Table 2). Local invasion on imaging ($P <$

0.001) and ureteroscopy high-grade (P = 0.003), but not hydronephrosis (P = 0.30), were significantly associated with NOC-UTUC (Table 2). There was no evidence that tumour location was associated with increased risk of pT2+ (P = 0.3) or NOC-UTUC (P = 0.6). When local invasion on imaging, hydronephrosis, tumour location and ureteroscopy high-grade were included together in multivariable models to predict pT2+ and NOC-UTUC, the estimates were not importantly changed, although hydronephrosis no longer reached statistical significance in its association with pT2+ (P = 0.065) (Table 3).

The AUC of a multivariable model that included only ureteroscopy high-grade and tumour location (based on ureteroscopy alone) to predict pT2+ was 0.66. With the addition of two imaging variables, local invasion on imaging and hydronephrosis, discrimination improved (AUC 0.71, likelihood ratio P value for improvement in model fit over ureteroscopy-alone model = 0.003). When the model was used to predict NOC-UTUC, the AUC of ureteroscopy high-grade and tumour location alone was 0.64. This improved to 0.70 with the addition of local invasion on imaging and hydronephrosis (likelihood ratio P value for improvement in model fit over ureteroscopy-alone model = 0.001).

We tested the interaction between hydronephrosis and tumour location. The interaction term was not statistically significant (P = 0.6). When we ran the analyses stratified by tumour location there was no difference in the effect of hydronephrosis on outcomes. Moreover, including the interaction term in a model with hydronephrosis and tumour location did not importantly improve the AUC.

Table 4 shows the predicted and actual risks of each outcome based on preoperative grade and local invasion on imaging; the two variables that were independently and significantly associated with all outcomes. Overall, predicted risks were similar to actual risks. However, our model overestimated the effect of local invasion on imaging among patients with low preoperative grade for both pathological outcomes.

TABLE 1 Summary of patient characteristics

Variable	Value
N	274
Median, interquartile range:	
Age at surgery, years	72 (63–77)
Body mass index, kg/m^2	27 (24–30)
N (%):	
Male gender	171 (62)
Tumour location	
Not seen	10 (4)
Pelvis	181 (66)
Ureter	83 (30)
Local invasion on imaging (n = 269)	41 (15)
Hydronephrosis on imaging (n = 272)	139 (51)
Cytology	
Negative	58 (21)
Positive	203 (74)
Not done	13 (5)
Ureteroscopy high-grade (n = 172)*	120 (70)
Previous non-muscle invasive bladder cancer	93 (34)
Pathological T stage	
≤pT1	141 (51)
pT2	58 (21)
≥pT3	75 (27)

*Local invasion on imaging = parenchymal, renal sinus fat or periureteric invasion. *Because we only have ureteroscopy biopsy data for 172 patients, all models that include preoperative high-grade as a predictor are limited to this subgroup.*

DISCUSSION

Improved patient selection for conservative management, neoadjuvant chemotherapy, and/or extended lymphadenectomy is urgently needed. The current mainstay of clinical staging for UTUC is comprised of pathological examination of the ureteroscopic specimen and imaging studies. However, clinical staging is frequently discordant with the final pathological stage at RNU [2,26]. In lower tract UC, which shares the same biology, pathological upstaging to pT3 and/or N+ disease occurs in up to 60% of patients [2,26]. Therefore, novel tools

TABLE 2 Univariate predictors of muscle-invasive (pT2+) or NOC-UTUC (pT3+ or N+) in patients with UTUC managed with RNU

	Muscle-invasive UTUC (pT2+)			NOC-UTUC (pT3+ or N+)		
	AUC	OR (95% CI)	*P*	AUC	OR (95% CI)	*P*
Ureteroscopy high-grade*	0.607	2.92 (1.45, 5.87)	0.023	0.620	3.86 (1.60–9.28)	0.003
Tumour location	0.545		0.3	0.530		0.6
None		Ref			Ref	
Ureter		1.27 (0.35–4.65)			0.67 (0.182–2.48)	
Pelvis		1.86 (0.49–7.10)			0.54 (0.14–2.10)	
Hydronephrosis on imaging	0.578	1.87 (1.16–3.03)	0.011	0.536	1.33 (0.79–2.24)	0.3
Local invasion on imaging	0.584	4.11 (1.92–8.79)	<0.001	0.605	4.34 (2.17–8.65)	<0.001

*OR, odds ratio; Ref, reference.Local invasion on imaging = parenchymal, renal sinus fat or periureteric invasion. *Because we only have ureteroscopy biopsy data for 172 patients, all models that include preoperative high grade as a predictor are limited to this subgroup.*

are needed to allow accurate staging that would result in individualized counselling and improved disease management.

We developed a highly accurate preoperative multivariable model to predict pT2+ and NOC-UTUC based on standard imaging and ureteroscopy features. Both local invasion on preoperative imaging and high-grade disease on ureteroscopy were strong, independent predictors of advanced pathological stage. According to our predictive model, a patient with high-grade UTUC on ureteroscopy and the presence of local invasion on imaging has a probability of 82% for pT2+ and 76% for NOC-UTUC. The predictive accuracy of the model was 70% for prediction of NOC-UTUC and 71% for pT2+. We showed that the accuracy in predicting pT2+ significantly improved from 66% with ureteroscopic variables alone to 71% with the combined ureteroscopy and imaging variables. Similar improvement was also seen for the prediction of NOC-UTUC (from 64% to 70%). Others investigators have already described the importance of combining preoperative variables such as hydronephrosis on imaging, ureteroscopy grade, and urinary cytology to increase the accuracy in identifying patients at risk for locally advanced disease [27]. Brien *et al.* [27] for example, reported that ureteroscopy high-grade was associated with pT2+ and NOC-UTUC in a multi-institutional study of 469 UTUCs. Margulis *et al.* [26] achieved a 76% prediction accuracy when they combined three ureteroscopic variables (location, grade, and architecture of the tumour) into a preoperative nomogram for prediction of NOC-UTUC. The authors selected the predictors in the final model based on how well each variable improved the predictive accuracy; we, in contrast, pre-specified our predictors. While such stepwise backwards selection techniques are not necessarily wrong, they certainly have the potential to inflate accuracy estimates.

The preoperative tools for clinical stage prediction currently available for patients with UTUC are quite limited. While preoperative imaging is effective in identifying LN involvement or distant metastasis, its ability to predict primary tumour stage or degree of local invasion alone is weak. In small retrospective studies, CT accuracy for predicting pathological stage in patients with UTUC ranged from 52% to 59% [28,29]. In contrast, multi-phase multi-detector-row CT in the staging of UTUC was shown to have an accuracy of 66% for locally advanced tumours and 96% in organ-confined disease [30]. Some studies have suggested a good correlation between ureteroscopic biopsy and pathological findings. For example, in a study of 42 patients, Keeley *et al.* [31] used ureteroscopy high-grade to predict pT2+ with an accuracy of 68%. Brown *et al.* [32] reviewed 119 patients and reported that biopsy high-grade had a positive predictive value of 66% for pT2+ but only 42% for pT3+. In contrast, Guarnizo *et al.* [33]. described less impressive results where 22% of the patients were understaged with ureteroscopic biopsy; 45% of biopsy stage Ta lesions were up-staged when final pathological specimens were examined. Although imaging and ureteroscopy variables separately may be insufficient to stage UTUC lesions accurately, we have shown that combining this information into a multivariable model improves overall predictive accuracy.

However, the present study has several limitations. It represents a retrospective analysis of a database from a single institution and, thus, our results are subject to the inherent biases associated with high-volume, tertiary care centres. The relatively few patients with all variables available for analysis in the multivariable model may also limit further associations. We failed to capture other features such as tumour size and multifocality, which could add predictive value. Widespread applicability of the present model will depend on external validation. Despite these limitations, the present study possesses several strengths, including centralized pathological and radiographic evaluation, as well as standardized management and follow-up, which are difficult to achieve in multi-institutional studies.

In conclusion, the present study developed a preoperative multivariable model that allows accurate staging of patients with UTUC. Our model can help identify patients with pT2+ disease and NOC-UTUC based on readily available imaging and ureteroscopic parameters. We also showed that combining

TABLE 3 Multivariable predictors of muscle-invasive UTUC (pT2+) or NOC-UTUC (pT3+ or N+) for 172 patients managed with RNU

	Muscle-invasive UTUC (pT2+)		NOC-UTUC (pT3+ or N+)	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Ureteroscopy high-grade	3.01 (1.42–6.37)	0.004	3.73 (1.49–9.35)	0.005
Tumour location:		0.6		0.7
None	Ref	Ref	Ref	Ref
Ureter	1.01 (0.22–4.73)		0.50 (0.10–2.36)	
Pelvis	1.55 (0.31–7.76)		0.60 (0.12–3.09)	
Hydronephrosis on imaging	2.01 (0.96–4.22)	0.065	1.42 (0.63–3.17)	0.4
Local invasion on imaging	3.61 (1.26–10.3)	0.017	5.39 (1.97–14.8)	0.001

OR, odds ratio; Ref, reference; Local invasion on imaging = parenchymal, renal sinus fat or periureteric invasion.

TABLE 4 Predicted (left) and actual (right) probabilities (%) of muscle-invasive UTUC or NOC-UTUC as a function of preoperative grade and parenchymal invasion

	Preoperative grade	
	Low	High
Muscle-invasive UTUC:		
No local invasion on imaging	25/26	49/49
Local invasion on imaging	54/40	78/82
NOC-UTUC		
No local invasion on imaging	11/13	32/31
Local invasion on imaging	39/20	71/76

Local invasion on imaging = parenchymal, renal sinus fat or periureteric invasion.

imaging and ureteroscopy variables was more accurate than ureteroscopy alone. Further research is needed to determine whether use of this predictive model to select patients for conservative management vs RNU, neoadjuvant chemotherapy, and/or extended LN dissection at the time of RNU will improve patient outcomes.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: **(UT)UC**, (upper tract) urothelial carcinoma; **RNU**, radical nephroureterectomy with excision of the bladder cuff; **LN**, lymph node; **NOC**, non-organ-confined; **MSKCC**, Memorial Sloan-Kettering Cancer Center; **AUC**, area-under-the-curve.