Postoperative Nomogram for Disease Recurrence and Cancer-Specific Death for Upper Tract Urothelial Carcinoma: Comparison to American Joint Committee on Cancer Staging Classification

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Purpose: We sought to develop prognostic models to predict disease recurrence and cancer-specific mortality in patients with upper tract urothelial carcinoma (UTUC) who underwent radical nephroureterectomy (RNU).

Materials and Methods: Data on 253 patients treated with RNU between 1995 and 2008 at a single high-volume tertiary referral center were analyzed. Statistically and clinically significant patient and tumor characteristics were identified in a univariate analysis and incorporated into a multivariable Cox regression model. The model was compared to the 2010 American Joint Committee on Cancer (AJCC) staging classification using the concordance index (c-index), corrected for statistical optimism using bootstrap methods.

Results: Five-year recurrence-free survival (RFS) and cancer-specific survival (CSS) rates were 73% [95% confidence interval (CI): 66-79%)] and 78% (95% CI: 71-84%), respectively. On multivariate analysis, higher preoperative glomerular filtration rate (GFR) was associated with better CSS [hazard ratio (HR) per 1 mL/min/m^2 increase in GFR for CSS: 0.74; $P = .002$)], while higher pathologic stage (HR for pT2: 2.99 and for ≥ pT3: 7.34; $P < .001$) and lymph node involvement (HR: 3.75; $P < .001$) were associated with worse CSS; results were similar for RFS. The ability of the final models, which included preoperative GFR, lymph node status, pathologic grade, and stage, to predict RFS and CSS (c-index 0.82 and 0.83, respectively) was similar to that of the 2010 AJCC staging classification (c-index 0.80 and 0.81, respectively).

Conclusion: Given the data-dependent selection of variables in this single institution cohort, it is unlikely that the marginal improvement found with these prediction models would importantly impact clinical decision-making or improve patient care. The 2010 AJCC staging classification alone is very accurate and should continue to guide follow-up after RNU.

Keywords: nomograms; prognosis; survival; urologic neoplasms; urothelium; carcinoma; transitional cell; retrospective studies.

INTRODUCTION

Upper tract urothelial carcinoma (UTUC) is a relatively rare neoplasm and accounts for 5-6% of all urothelial tumors.[1] Radical nephroureterectomy (RNU) with bladder cuff removal is the most effective treatment for invasive UTUC. Approximately 20-40% of patients initially present with locally advanced disease and lymph node metastases at the time of diagnosis.[2] Despite advances in surgical technique, 5-year cancer-specific mortality rates are 15%, 45% and 88% for patients with pT2N0, pT3N0 and pT4N0 disease, respectively.[3] The rarity of the disease has limited the use of prospective studies to evaluate the role of a multimodality treatment approach, and existing data indicate that the survival rates in these patients have not improved.[4]

Accurate prediction of postoperative cancer recurrence and survival outcomes could help guide decisions regarding administration of adjuvant chemotherapy and selective enrollment into clinical trials of novel therapies. Currently, use of adjuvant chemotherapy is limited by the lack of proof of efficacy and potential side effects. Moreover, physicians are hesitant to administer neoadjuvant chemotherapy because of the limited accuracy of preoperative staging based on histopathology. The pathological staging criteria defined by the American Joint Committee on Cancer (AJCC) incorporate tumor stage, nodal stage, and metastases information to predict prognosis.[5] However, application of the 2010 AJCC staging classification to UTUC is limited for several reasons. First, lymph node status is not consistent in UTUC as there is no consensus defining an anatomic template for a lymph node dissection and nearly 60% of patients do not have adequate lymph node staging.[6] Second, tumor grade, which is an important predictor of prognosis for UTUC, is not included in the 2010 AJCC classification.[7,8]

Given these putative limitations of the 2010 AJCC staging classification, our objective was to develop multivariable models to predict five-year recurrence-free survival (RFS) and cancer-specific survival (CSS) after RNU based on patient and tumor characteristics and to compare its prognostic accuracy to that of the 2010 AJCC staging classification.

MATERIALS AND METHODS

Patient Cohort

In this institutional review board-approved study, we reviewed all the prospectively collected data on 324 consecutive patients with upper tract tumors treated with RNU at Memorial Sloan-Kettering Cancer Center (MSKCC) between 1995 and 2008. We excluded patients who underwent previous or concurrent radical cystectomy (n = 46), had prior contralateral UTUC (n = 4), or received preoperative chemotherapy (n = 21). The remaining 253 patients were the subjects of the present analysis. RNU was performed by genitourinary surgeons at MSKCC using a standardized approach, including the removal of the kidney with the entire length of the ureter and the adjacent segment of the bladder cuff. The hilar and regional lymph nodes adjacent to the ipsilateral great vessel generally were resected. All patients were enrolled in standardized post-operative clinical pathways. The preoperative evaluation was similar among all patients, including computed tomography (CT) scan, chest X-ray, cysto-ureteroscopy, and urine cytology. No patient received preoperative chemotherapy and post-operative chemotherapy consisted of platinum-based treatment for evidence of metastatic disease.

Outcome Evaluation

To determine RFS, we defined disease recurrence as any radiographic documentation of disease or pathologically proven failure in operative site, regional lymph nodes, or distant metastasis. Recurrences within the bladder and the contralateral collecting system were not considered in the analysis of RFS rate. To determine CSS, cause of death was determined by chart review corroborated by death certificate.

Statistical Analysis

Our first aim was to identify postoperative predictors of oncologic outcome after RNU. We used univariate Cox proportional-hazards regression models to predict RFS and CSS. Predictors in our analyses included gender, age, American Society of Anesthesiologists (ASA) classification score, preoperative glomerular filtration rate (GFR), smoking history, carcinoma in situ, multifocal disease, pathologic grade (≥ 2 or < 2), pathologic stage ($\leq$ pT1, pT2, or $\geq$ pT3) and node status (NX, N0, or N1). For the outcomes of RFS and CSS, we created two multivariable models that included carcinoma in situ, grade, pathologic stage, and node status. Predictors for the multivariable models were chosen from those found to be significant on univariate analyses; due to the limited number of events, we focused our selection on those that were deemed the most clinically relevant. We evaluated the predictive accuracy of our multivariable models using concordance index (c-index) with bootstrapping to correct for statistical

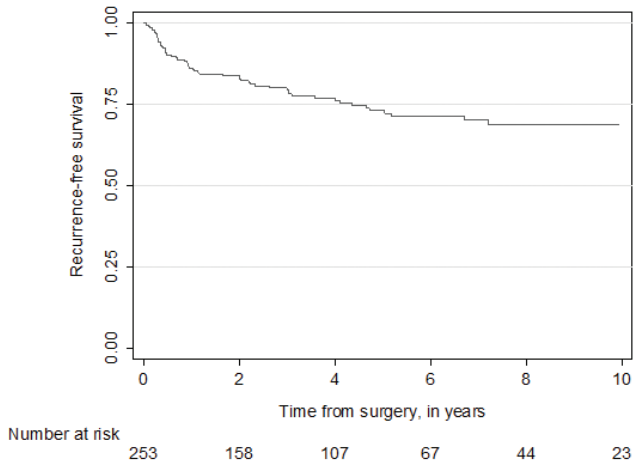

Figure 1. Recurrence-free survival in patients with upper tract urothelial carcinoma treated with radical nephroureterectomy and bladder cuff excision.

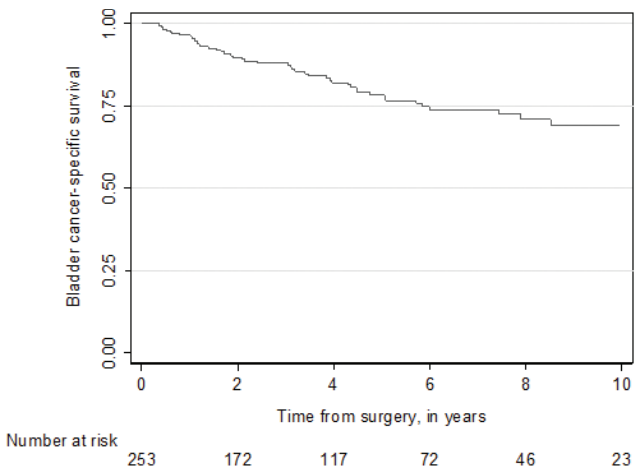

Figure 2. Cancer-specific survival in patients with upper tract urothelial carcinoma treated with radical nephroureterectomy and bladder cuff excision.

optimism. All statistical analyses were conducted using STATA 11.0 (StataCorp, College Station, TX, USA).

RESULTS

Patient characteristics are shown in Table 1. The median age of patients was 72 years; approximately two-thirds (62%; n = 158) of patients were male and three-quarters reported a history of smoking (74%). The median follow-up for patients without disease recurrence or death was 4.2 years. Of the 58 patients who experienced recurrence, 48 died from UTUC including 1 patient who died from disease without prior evidence of a recurrence and was considered to have experienced recurrence at the time of death. Overall, the 5-year probability of RFS and CSS were 73% [(95% confidence interval (CI): 66-79%)] and 78% (95% CI: 71-84%), respectively (Figures 1 and 2). In total, 96 patients died; the 5-year survival probability was 65% (95% CI: 58-72%).

Table 2 shows the results from the univariate Cox proportional-hazards (HR) regression models. Age, ASA score, and preoperative GFR were significantly associated with CSS. Additionally, grade, pathologic stage, and node status were significantly associated with RFS and CSS. We did not find any evidence that gender (all $P \geq .2$), or smoking history (all $P \geq .4$) were significantly associated with any of the outcomes. There was no evidence of non-linearity with respect to age and preoperative GFR.

The multivariable results are shown in Table 3. Higher preoperative GFR was associated with better outcomes, while higher grade, pathologic stage, and lymph node involvement were significantly associated with worse outcomes.

We were concerned that given the high rate of death from other causes (half the deaths were due to causes other than UTUC), a competing-risks regression model would have been more appropriate. We repeated all of our analyses using a competing risk regression models and found very similar results. For example, the subhazard ratio for the effect of GFR on recurrence was 0.74 (95% CI: 0.61-0.90) compared to HR of 0.73 (95% CI: 0.61-0.88) using the Cox proportional-hazards model; both the subhazard ratio and HR estimate for pathologic stage pT3 and death from disease were 7.34. Given the similarity in estimates and the ability to compare concordance indices, we chose to present our results from the Cox proportional-hazards models.

The overall discriminatory ability of our two multivariable models to predict RFS and CSS was high (bootstrap-corrected c-index: 0.82 and 0.83, respectively). In comparison, the discriminatory ability of AJCC stage alone to predict RFS and CSS as measured by the bootstrap-corrected c-index was 0.80 and 0.81, respectively.

DISCUSSION

In this study, we combined patient and tumor characteristics with pathologic stage and grade to predict RFS and CSS. Additional patient characteristics and histology grade only

Table 1. Patient characteristics. All values are median (IQR) or frequency (proportion).

Variables	No. = 253
Age at surgery (years)	72 (63-77)
Body mass index (n = 246) (kg/m^2)	27 (24-30)
Male gender	158 (62%)
Preoperative GFR (n = 248) (mL/min/m^2)	54 (44-68)
Preoperative high grade (n = 161)	110 (68%)
Hematuria, no. (%)	
None	64 (25)
Micro	28 (11)
Gross	161 (64)
Parenchymal invasion on CT (n = 248)	36 (15%)
Hydronephrosis on CT (n = 251)	125 (50%)
Cytology, no. (%)	
Negative	52 (21)
Positive	190 (75)
Not done	11 (4)
Smoking history* (n = 252)	185 (73%)
ASA score (n = 252), no. (%)	
1	7 (3)
2	127 (50)
3	118 (47)
Pathologic stage, no. (%)	
≤ pT1	132 (52)
pT2	56 (22)
≥ pT3	65 (26)
Lymph node status, no. (%)	
NX	93 (37)
N0	137 (54)
N1	23 (9)
Pathologic grade (n = 252), no. (%)	
High	193 (77)
Low	59 (23)
Previous NMIBC	86 (34)
CIS	70 (28)
Multifocal disease (n = 250)	65 (26%)

Keys: NMIBC, non-muscle invasive bladder cancer; CIS, carcinoma in situ; GFR, glomerular filtration rate; IQR, interquartile range; CT, computed tomography; ASA, American Joint Committee on Cancer.
*Smoking history reported at time of surgery (current/former vs. never).

marginally enhanced the discriminatory ability of the 2010 AJCC staging classification to predict disease recurrence and cancer-specific mortality in UTUC patients treated with RNU. Given that the cohort was derived from a single institution and that variables were selected for the multivariable models in a data-dependent manner, we are cautious to recommend the implementation of our models and replacing the standard AJCC stage classification. As such, the incorporation of GFR, pathologic grade, and nodal status in a formal prognostic model is unlikely to importantly impact clinical decision-making or improve patient care.

Prediction models have been developed for various tumors to assist physicians, provide patients with estimates of clinical outcomes, and aid in decision making. There is evidence that incorporating multiple variables into a prediction model provides more accurate risk prediction than classifying patients based on tumor stage alone. In urologic oncology, multivariable models have been shown to be more accurate than clinical staging in predicting cancer-specific mortality for renal cell carcinoma, urothelial carcinoma of the bladder, prostate cancer, and penile cancer.[9-12] It is important to evaluate the clinical value of a new prediction model before it is implemented into clinical practice. One of the primary steps is to compare its discriminatory ability with that of what is currently used. Then, a direct comparison should be conducted in an external cohort using calibration and decision curve analytic techniques to determine if the new predictive outperforms other models.[13]

Recently, Jeldres and colleagues developed a multivariable predictive model in UTUC incorporating age, pathological stage, and tumor grade using the Surveillance, Epidemiology, and End Results (SEER) database.[6] Their model's accuracy to predict cancer-specific mortality after RNU was good (75.4%) and demonstrated statistically superior discriminatory ability compared to the AJCC and Union for International Cancer Control (UICC) staging classification (64.8%). Jeldres and colleagues acknowledged the limitations inherent within the SEER database including lack of central pathology review, incomplete surgical resection of a bladder cuff in 31-35% of patients and absence of a lymph node dissection in approximately 60% of patients. The incompleteness of surgical treatment defined by the lack of bladder cuff excision can negatively impact the accuracy of pathological staging and may limit the generalizability of the results.

Using a contemporary cohort of patients, we developed prognostic models to predict disease recurrence and cancer-specific mortality incorporating pathologic stage, lymph node status, tumor grade, and preoperative GFR. Preoperative GFR is an effective surrogate for overall health as multiple stud-

Table 2. Univariate Cox proportional-hazards models for recurrence-free survival and upper tract urothelial carcinoma-specific survival.

Variables	Recurrence-Free Survival			Disease-Specific Survival		
	HR	95% CI	*P*	HR	95% CI	*P*
Male	1.11	0.65-1.89	.7	1.21		.5
Age	1.22	0.97-1534	.097	1.44		.014
ASA Score			.074			.037
< 3	Ref	Ref		Ref		
≥ 3	1.60	0.96-2.67		1.84		
Preoperative GFR (per 10 mL/min/m^2)	0.76	0.64-0.89	< .001	0.74		.002
Smoking	0.77	0.44-1.35	.4	0.77		.4
CIS	1.63	0.96-2.79	.072	1.66		.094
Multifocal disease	0.91	0.50-1.66	.8	0.88		.7
Grade			.005			.014
Low	Ref	Ref		Ref		
High	3.36	1.44-7.83		2.92		
Pathologic stage			< .001			< .001
≤ pT1	Ref	Ref		Ref		
pT2	2.72	1.22-6.05		4.21		
≥ pT3	8.91	4.61-17.2		11.7		
Node status			< .001			< .001
N0	Ref	Ref		Ref		
N1	8.01	4.26-15.1		7.99		
NX	0.78	0.42-1.46		0.76		

Keys: HR, hazard ratio; CI, confidence interval; Ref, reference; NMIBC, non-muscle invasive bladder cancer; CIS, carcinoma in situ; Smoking, smoking status at time of surgery; GFR, glomerular filtration rate, ASA, American Joint Committee on Cancer.

ies have demonstrated that renal function impacts mortality and reduced renal function leads to hypertension, anemia, malnutrition, cardiovascular disease, and reduced quality of life.[14] In UTUC, assessment of renal function is important for prognosis because RNU is the most effective treatment for invasive disease while adjuvant chemotherapy is limited by an increased risk of renal dysfunction. Furthermore, and in contrast to the SEER study, we evaluated a consecutive, prospectively collected cohort of patients in a single, high-volume tertiary referral center. In addition, the c-index for the AJCC staging classification in the SEER database was low (RFS: 64.8%) and in our model, the 2010 AJCC staging classification was highly predictive of survival outcomes (RFS: 80%, CSS: 81%). These results might be explained by the heterogeneity in bladder cuff excision and lymphadenectomy within the SEER database.

We failed to find evidence that the addition of grade, GFR, and lymph node status importantly improved prediction of oncologic outcomes in UTUC. Despite a marginal improvement in the discriminatory ability of our predictive models compared with the 2010 AJCC staging classification, we are cautious with the interpretation of our results. In this single institution study that involved data-dependent variable selection, a small change in effect size is unlikely to withstand a comparative analysis with the standard AJCC staging classification in an external cohort using calibration and decision curve analytic techniques as benchmarks. Alternatively, if we had achieved these results using a large, multi-institutional database, then a small improvement in the c-index would be more clinically dependable and worthy of further investigation.

There are several important limitations of our study. First, UTUC is a rare malignancy, which makes evaluation of large

Table 3. Multivariate Cox proportional-hazards models for recurrence-free survival and cancer-specific survival in patients with upper tract urothelial carcinoma treated with radical nephroureterectomy and bladder cuff excision.

Variables	Recurrence-Free Survival			Disease-Specific Survival		
	HR	95% CI	*P*	HR	95% CI	*P*
Preoperative GFR (per 10 mL/min/m^2)	0.73	0.61-0.88	< .001	0.74	0.61-0.90	.002
Tumor grade			.2			.3
Low	Ref	Ref		Ref	Ref	
High	1.77	0.72-4.38		1.69	0.69-4.17	
Pathologic Stage			< .001			< .001
≤ pT1	Ref	Ref		Ref	Ref	
pT2	1.67	0.71-3.94		2.99	1.12-7.97	
≥ pT3	5.71	2.77-1.7		7.34	2.98-18.1	
Node Status			< .001			.002
N0	Ref	Ref		Ref	Ref	
N1	3.95	1.98-7.86		3.75	1.78-7.89	
NX	1.16	0.59-2.29		1.31	0.61-2.81	

Keys: HR, hazard ratio; CI, confidence interval; Ref, reference; GFR, glomerular filtration rate.

patient populations difficult. However, in spite of the limited size of our cohort, we were able to identify several clinically relevant predictors. Critically, despite identifying several variables that were independently and statistically significant on multivariable analysis, incorporation of these factors into a prediction model did not importantly improve the predictive accuracy above that of the 2010 AJCC staging alone. Second, tumor grade and pathology were determined by institutional pathology report, as there was no systematic re-review of the pathologic material. Third, despite the standardization of surgical technique and routine excision of a bladder cuff during RNU, 37% of the patients in our cohort did not receive a lymphadenectomy. Therefore, we believe it is important to emphasize the need for a standardization of the extent of lymph node dissection and its indications in UTUC patients treated with RNU.

We believe our study is novel and emphasizes the importance of considering the impact of a prediction model on clinical decision making rather than focusing on marginal statistical significance. Furthermore, our study will help investigators develop an improved prediction model by incorporating novel biomarkers for disease progression such as tumor architecture.[15] In the future, the evaluation of a larger multi-institutional database with additional patient and tumor characteristics may improve the discriminatory ability of a predictive model for UTUC. However, we demonstrated that in this contemporary cohort of UTUC patients treated with RNU the incorporation of multiple clinically significant predictors does not provide more accurate prognostic information than pathologic stage.

CONCLUSION

The multivariate prognostic model we developed incorporating GFR, tumor grade, stage and lymph node status did not meaningfully improve the discriminatory ability of the 2010 AJCC staging classification for UTUC. In this patient cohort, the 2010 AJCC staging classification alone was very accurate. The 2010 AJCC staging classification should be used to guide follow-up after RNU and to assist physicians in providing estimates of cancer-specific outcomes to their patients.

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CONFLICT OF INTEREST

None declared.

REFERENCES

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010;60:277-300.
2. Munoz JJ, Ellison LM. Upper tract urothelial neoplasms: incidence and survival during the last 2 decades. J Urol. 2000;164:1523-5.
3. Margulis V, Shariat SF, Matin SF, et al. Outcomes of radical nephroureterectomy: a series from the Upper Tract Urothelial Carcinoma Collaboration. Cancer. 2009;115:1224-33.
4. Lughezzani G, Jeldres C, Isbarn H, et al. Nephroureterectomy and segmental ureterectomy in the treatment of invasive upper tract urothelial carcinoma: a population-based study of 2299 patients. Eur J Cancer. 2009;45:3291-7.
5. Edge SB, David; Compton, Carolyn; Fritz, April; Greene, Frederick; Trotti III, Andy. AJCC Cancer Staging Manual. Springer, New York, NY. 2010; 7th edition.
6. Jeldres C, Sun M, Lughezzani G, et al. Highly predictive survival nomogram after upper urinary tract urothelial carcinoma. Cancer. 2010;116:3774-84.
7. Brown GA, Matin SF, Busby JE, et al. Ability of clinical grade to predict final pathologic stage in upper urinary tract transitional cell carcinoma: implications for therapy. Urology. 2007;70:252-6.
8. Hall MC, Womack S, Sagalowsky AI, Carmody T, Erickstad MD, Roehrborn CG. Prognostic factors, recurrence, and survival in transitional cell carcinoma of the upper urinary tract: a 30-year experience in 252 patients. Urology. 1998;52:594-601.
9. Karakiewicz PI, Briganti A, Chun FK, et al. Multi-institutional validation of a new renal cancer-specific survival nomogram. J Clin Oncol. 2007;25316-22.
10. Shariat SF, Karakiewicz PI, Palapattu GS, et al. Nomograms provide improved accuracy for predicting survival after radical cystectomy. Clin Cancer Res. 2006;12:6663-76.
11. Zini L, Cloutier V, Isbarn H, Perrotte P, et al. A simple and accurate model for prediction of cancer-specific mortality in patients treated with surgery for primary penile squamous cell carcinoma. Clin Cancer Res. 2009;15:1013-8.
12. Stephenson AJ, Scardino PT, Eastham JA, et al. Postoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. J Clin Oncol. 2005;23:7005-12.
13. Lughezzani G, Budaus L, Isbarn H, et al. Head-to-head comparison of the three most commonly used preoperative models for prediction of biochemical recurrence after radical prostatectomy. Eur Urol. 2010;57:562-8.
14. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351:1296-305.
15. Fritsche HM, Novara G, Burger M, et al. Macroscopic sessile tumor architecture is a pathologic feature of biologically aggressive upper tract urothelial carcinoma. Urol Oncol. 2012;30:666-72.