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Urothelial Cancer

Predicting Clinical Outcomes After Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma

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Abstract

Background: Novel prognostic factors for patients after radical nephroureterectomy (RNU) for upper tract urothelial carcinoma (UTUC) have recently been described.
Objective: We tested the prognostic value of pathologic characteristics and developed models to predict the individual probabilities of recurrence-free survival (RFS) and cancer-specific survival (CSS) after RNU.
Design, setting, and participants: Our study included 2244 patients treated with RNU without neoadjuvant or adjuvant therapy at 23 international institutions. Tumor characteristics included T classification, grade, lymph node status, lymphovascular invasion, tumor architecture, location, and concomitant carcinoma in situ (CIS). The cohort was randomly split for development (12 centers, $n = 1273$) and external validation (11 centers, $n = 971$).
Interventions: All patients underwent RNU.
Measurements: Univariable and multivariable models addressed RFS, CSS, and comparison of discrimination and calibration with American Joint Committee on Cancer (AJCC) stage grouping.

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Results and limitations: At a median follow-up of 45 mo, 501 patients (22.3%) experienced disease recurrence and 418 patients (18.6%) died of UTUC. On multivariable analysis, T classification (p for trend <0.001), lymph node metastasis (hazard ratio [HR]: 1.98; $p = 0.002$), lymphovascular invasion (HR: 1.66; $p < 0.001$), sessile tumor architecture (HR: 1.76; $p < 0.001$), and concomitant CIS (HR: 1.33; $p = 0.035$) were associated with disease recurrence. Similarly, T classification (p for trend < 0.001), lymph node metastasis (HR: 2.23; $p = 0.001$), lymphovascular invasion (HR: 1.81; $p < 0.001$), and sessile tumor architecture (HR: 1.72; $p = 0.001$) were independently associated with cancer-specific mortality. Our models achieved 76.8% and 81.5% accuracy for predicting RFS and CSS, respectively. In contrast to these well-calibrated models, stratification based upon AJCC stage grouping resulted in a large degree of heterogeneity and did not improve discrimination.

Conclusions: Using standard pathologic features, we developed highly accurate prognostic models for the prediction of RFS and CSS after RNU for UTUC. These models offer improvements in calibration over AJCC stage grouping and can be used for individualized patient counseling, follow-up scheduling, risk stratification for adjuvant therapies, and inclusion criteria for clinical trials.

1. Introduction

Evidence-based data to guide risk-stratified clinical decision making following radical nephroureterectomy (RNU), the surgical standard of care for upper tract urothelial carcinoma (UTUC), are sparse and are limited by homogeneous study populations with small case numbers. Several recent multi-institutional studies have identified prognostic factors for outcomes following RNU that supplement the traditional pathologic T and N categories and tumor grade [1–9].

While a recent study reported that the combination of clinical factors with basic pathologic criteria improved prediction of cancer-specific survival (CSS) as compared to models based solely on pathologic staging [2], it failed to incorporate many of the recently published prognostic clinicopathologic variables. Age, gender, lymphovascular invasion (LVI), sessile tumor architecture, and concomitant carcinoma in situ (CIS) have been identified as potential prognostic factors associated with outcomes following RNU for UTUC [2–9].

Improved risk stratification and accurate individualized prediction of postoperative recurrence and survival outcomes can help guide patient counseling, follow-up scheduling, administration of adjuvant therapies, and design of clinical trials. Prognostic models have been developed for a variety of malignancies and are used for clinical decision making at different disease states [10,11]. We developed and validated multivariable models including the aforementioned clinicopathologic characteristics to predict recurrence-free survival (RFS) and CSS after RNU for UTUC. The calibration of these models was compared to that of AJCC staging.

2. Patients and methods

2.1. Patient selection

This was an institutional review board–approved study with all participating sites providing the necessary institutional data-sharing agreements prior to initiation of the study. Twenty-three international centers provided data. A computerized databank was generated for data transfer. After combining the data sets, reports were generated for each variable to identify data inconsistencies and other data integrity problems. Through regular communication with all sites, resolution of all identified anomalies was achieved before analysis. Prior to final analysis, the database was frozen and the final data set was produced.

The study population comprised 2244 patients with UTUC who underwent open or laparoscopic RNU between 1987 and 2007. We excluded patients with a history of muscle-invasive urothelial carcinoma (UC) of the urinary bladder and those who received neoadjuvant or adjuvant therapies. Surgery was performed by surgeons according to the standard criteria for RNU, that is, extrafascial dissection of the kidney with the entire length of ureter and adjacent segment of the bladder cuff. The hilar and regional lymph nodes adjacent to the ipsilateral great vessel were generally resected if palpable intraoperatively or enlarged on preoperative axial imaging. The extent of lymphadenectomy performed was at the discretion of individual surgeons.

2.2. Pathologic evaluation

All surgical specimens were processed according to standard pathologic procedures at each institution. Pathologists, who were blinded to clinical outcomes, reexamined all specimens according to standardized criteria and confirmed UC histology. Tumors were staged according to the 2002 American Joint Committee on Cancer–International Union Against Cancer (AJCC/UICC) TNM classification [12]. Tumor grade was assessed according to the 1998 World Health Organization–International Society of Urologic Pathology consensus classification [13]. Tumor location was defined as either renal pelvic or ureteral. In tumors involving both the renal pelvis and ureter, the location was attributed to the index lesion, as defined by the most advanced stage and/or grade [14]. Tumor architecture was defined as papillary or sessile based on the predominant feature of the index lesion [6]. LVI was defined as the presence of tumor cells within an endothelium-lined space without underlying muscular walls [4].

2.3. Follow-up regimen

Patients were generally followed every 3–4 mo for the first year following RNU, every 6 mo from the second through the fifth year, and annually thereafter. Follow-up consisted of a history, physical examination, routine blood work, urinary cytology, chest radiography, cystoscopic evaluation of the urinary bladder, and radiographic evaluation of the contralateral upper urinary tract. Elective bone scans, chest

computed tomography, or magnetic resonance imaging were performed when clinically indicated.

Disease recurrence was defined as tumor relapse in the operative field, regional lymph nodes, and/or distant metastasis. Occurrences of UC in the bladder or contralateral upper tract were not coded as disease recurrence. Cause of death was determined by the treating physicians, by chart review corroborated by death certificates, or by death certificates alone. To reduce bias in attribution of cause of death, only patients who had UC listed on the death certificate were considered to have died of UTUC for this study. All patients who were coded as dead of cancer had previous disease recurrence. Patients who died in the perioperative period (ie, within 30 d of surgery) were censored at time of death for UTUC-specific survival analyses.

2.4. Statistical analysis

The cohort was randomly split into two groups: one for development of the prognostic models, and the other for external validation. The development cohort was composed of 1273 patients from 12 centers. The external validation cohort was composed of 971 patients from 11 centers. The clinicopathologic characteristics of the development and external validation cohorts were compared using the student *t* test, chi-square test, and log-rank test. Univariable and multivariable Cox regression models addressed time to disease recurrence and cancer-specific mortality (CSM) after RNU.

Multivariable Cox regression coefficients were then used to generate prognostic nomograms. Predictive accuracy of these nomograms was

Table 1 – Clinicopathologic characteristics of the 2244 patients treated with radical nephroureterectomy for upper tract urothelial carcinoma

	Development cohort (*n* = 1273)	External validation cohort (*n* = 971)	Total (*n* = 2244)	*p* value
Age, yr, median (IQR)	69.0 (61.1–75.5)	70.5 (62.0–76.3)	69.9 (61.6–76.0)	0.052
Gender, *n* (%)				0.40
Male	861 (67.6)	641 (66.0)	1502 (66.9)	
Female	412 (32.4)	330 (34.0)	742 (33.1)	
Pathologic T classification, no. (%)				0.39
pT0	7 (0.5)	8 (0.8)	15 (0.7)	
pTa	305 (24.0)	211 (21.7)	516 (23.0)	
pTis	28 (2.2)	18 (1.9)	46 (2.0)	
pT1	309 (24.3)	228 (23.5)	537 (23.9)	
pT2	253 (19.9)	191 (19.7)	444 (19.8)	
pT3	333 (26.2)	273 (28.1)	606 (27.0)	
pT4	38 (3.0)	42 (4.3)	80 (3.6)	
Pathologic tumor grade, no. (%)				0.49
Low	242 (19.0)	164 (16.9)	406 (18.1)	
High	1031 (81.0)	807 (83.1)	1838 (81.9)	
Pathologic N classification, no. (%)				0.22
pN0	294 (23.1)	246 (25.3)	540 (24.1)	
pNx	912 (71.6)	663 (68.3)	1575 (70.2)	
pN1–3	67 (5.3)	62 (6.4)	129 (5.7)	
AJCC stage, no. (%)				0.66
0	7 (0.5)	7 (0.7)	14 (0.6)	
0a	303 (23.8)	208 (21.4)	511 (22.8)	
0is	28 (2.2)	18 (1.9)	46 (2.0)	
I	303 (23.8)	228 (23.5)	531 (23.7)	
II	242 (19.0)	184 (18.9)	426 (19.0)	
III	294 (23.1)	241 (24.8)	535 (23.8)	
IV	96 (7.5)	85 (8.8)	181 (8.1)	
Lymphovascular invasion, no. (%)				0.67
Absent	1006 (79.0)	776 (79.9)	1782 (79.4)	
Present	267 (21.0)	195 (20.1)	462 (20.6)	
Tumor architecture, no. (%)				0.08
Papillary	970 (76.2)	772 (79.5)	1742 (77.6)	
Sessile	303 (23.8)	199 (20.5)	502 (22.4)	
Concomitant CIS, no. (%)				0.65
Absent	1003 (78.8)	757 (78.0)	1760 (78.4)	
Present	270 (21.2)	214 (22.0)	484 (21.6)	
Tumor location, no. (%)				0.26
Renal pelvis	808 (63.5)	641 (66.0)	1449 (64.6)	
Ureter	465 (36.5)	330 (34.0)	795 (35.4)	
Previous bladder cancer, no. (%)				0.82
No	937 (73.6)	718 (73.9)	1655 (73.8)	
Yes	336 (26.4)	253 (26.1)	589 (26.2)	
Recurrence				0.36
Patients, no. (%)	277 (21.8)	224 (23.1)	501 (22.3)	
Median follow-up, mo (IQR)*	48.0 (22.0–82.0)	42.6 (20.0–86.4)	46.0 (20.7–83.9)	
Cancer-specific mortality				0.43
Patients, no. (%)	230 (18.1)	188 (19.4)	418 (18.6)	
Median follow-up, mo (IQR)*	47.0 (21.0–81.0)	42.0 (20.0–85.7)	45.0 (20.0–82.0)	

IQR = interquartile range; AJCC = American Joint Committee on Cancer; CIS = carcinoma in situ.
* For patients censored at last follow-up.

Table 2 – Univariable and multivariable Cox regression analyses assessing the association between predictor variables and disease recurrence and cancer-specific mortality in the development cohort of 1273 patients who underwent radical nephroureterectomy for upper tract urothelial carcinoma

	Recurrence				Cancer-specific mortality			
	Univariable		Multivariable		Univariable		Multivariable	
	HR	*p* value	HR	*p* value	HR	*p* value	HR	*p* value
Age, yr	1.02	<0.001	1.01	0.053	1.03	<0.001	1.02	0.004
Gender (female vs male)	1.21	0.132	–	–	1.07	0.638	–	–
Pathologic T classification	–	<0.001	–	<0.001	–	<0.001	–	<0.001
pTa	1.00	(referent)	1.00	(referent)	1.00	(referent)	1.00	(referent)
pTis	2.97	0.051	2.75	0.111	2.73	<0.001	2.43	0.212
pT1	1.63	0.110	1.29	0.600	1.52	0.210	1.08	0.884
pT2	4.73	<0.001	2.65	0.038	3.41	<0.001	2.17	0.116
pT3	9.61	<0.001	6.05	<0.001	11.80	<0.001	5.40	0.001
pT4	11.33	<0.001	12.78	<0.001	29.09	<0.001	8.37	<0.001
High tumor grade	6.32	<0.001	1.38	0.546	6.68	<0.001	1.69	0.352
Pathologic N classification	–	<0.001	–	0.007	–	<0.001	–	0.003
pN0	1.00	(referent)	1.00	(referent)	1.00	(referent)	1.00	(referent)
pNx	1.00	0.990	1.34	0.060	1.07	0.710	1.43	0.045
pN1-3	4.23	<0.001	1.98	0.002	4.99	<0.001	2.23	0.001
Lymphovascular invasion	3.70	<0.001	1.66	<0.001	4.01	<0.001	1.81	<0.001
Sessile tumor architecture	5.11	<0.001	1.76	<0.001	5.22	<0.001	1.72	0.001
Concomitant CIS	1.81	<0.001	1.33	0.035	1.76	<0.001	1.31	0.074
Tumor location	0.88	0.311	–	–	0.883	0.365	–	–
Previous bladder cancer	1.13	0.360	–	–	1.25	0.130	–	–
C-index (development cohort)				0.807				0.820
C-index (validation cohort)				0.768				0.815

HR = hazard ratio; CIS = carcinoma in situ.

quantified in the validation cohort using Harrell's concordance index (c-index) [15,16]. Calibration plots were generated to explore nomogram performance on the external validation cohort. All reported *p* values are two-sided, and statistical significance was set at 0.05. All statistical tests were performed with the R open-source statistical software package (www.r-project.org/). The nomograms were generated using the *Design* R package and calibration plots were generated using the *val.surv* method of the *rms* R package.

3. Results

The descriptive characteristics of the 2244 patients are shown in Table 1. Median age at RNU was 69.9 yr, and 67% of patients were male. Median follow-up was 45 mo (interquartile range: 20–80). Of the 2244 patients in the complete cohort, 501 (22.3%) experienced disease recurrence and

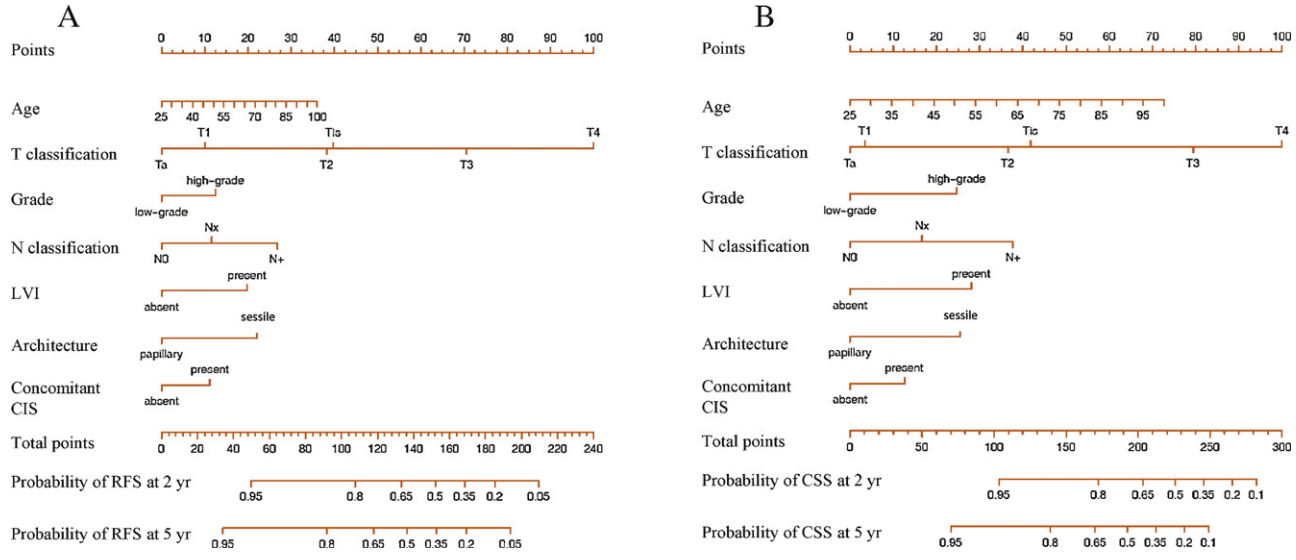

Fig. 1 – Nomograms for prediction of 2- and 5-yr (A) recurrence-free (RFS) and (B) cancer-specific survival (CSS) probabilities for patients following radical nephroureterectomy (RNU). Nomogram instructions: To obtain the nomogram-predicted probabilities of RFS and CSS after RNU, locate patient values on each axis. Draw a vertical line to the *Points* axis to determine how many points are attributed for each variable value. Sum the points for all variables. Locate the sum on the *Total Points* line to assess the individual probabilities for RFS and CSS at 2 and 5 yr following RNU.
LVI = lymphovascular invasion; CIS = carcinoma in situ.

418 (18.6%) died of UTUC. The development and external validation cohorts did not differ significantly in terms of clinicopathologic characteristics or outcomes.

Table 2 shows the univariable and multivariable Cox regression models for prediction of disease recurrence and CSM. On univariable analyses, age, T classification, grade, lymph node status, LVI, tumor architecture, and concomitant CIS were associated with disease recurrence (all p values <0.001). Gender, tumor location, and history of previous bladder cancer were not associated with disease recurrence. Multivariable analysis revealed that T classification, lymph node status, LVI, tumor architecture, and concomitant CIS were independently associated with disease recurrence (all p values <0.04). The accuracy of the multivariable model for predicting disease recurrence, as quantified by the c-index in the external validation cohort, was 76.8%.

In regard to CSM, univariable analyses revealed that age, T classification, grade, lymph node status, LVI, tumor architecture, and concomitant CIS were associated with CSM (all p values <0.001). Gender, tumor location, and history of previous bladder cancer were not associated with CSM. On multivariable analysis, age, T classification, lymph node status, LVI, and tumor architecture were independent predictors of CSM (all p values <0.005). The accuracy of the multivariable model for predicting CSM, as quantified by the c-index in the external validation cohort, was 81.5%.

The nomograms for the predictions of 2- and 5-yr probabilities for RFS and CSS are shown in Figure 1. Calibration plots revealed minimal under- and overestimation at all

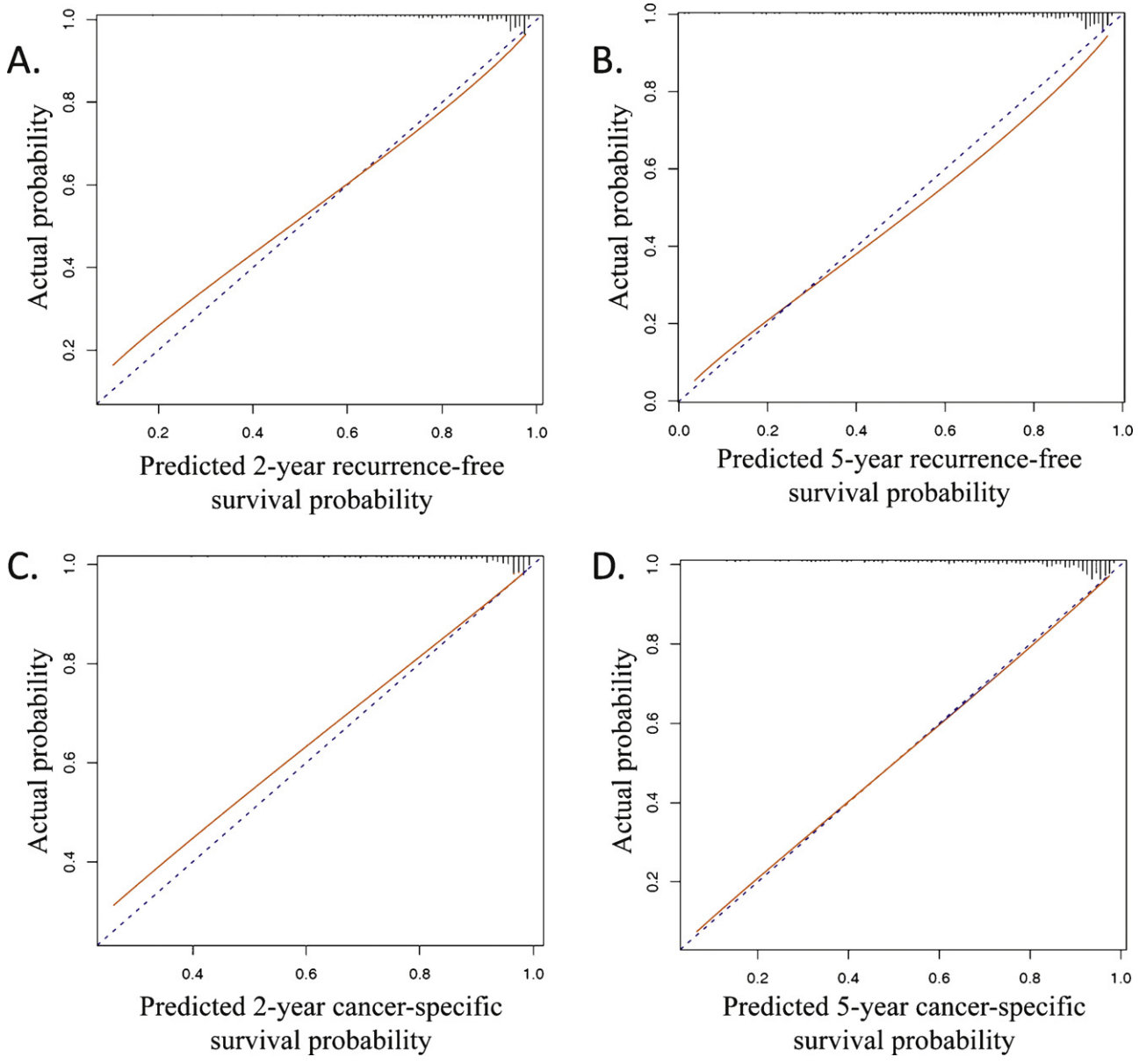

Fig. 2 – Calibration plots demonstrating the relationship between the nomogram-predicted 2- and 5-yr (A,B) recurrence-free (RFS) and (C,D) cancer-specific survival (CSS) probabilities and the observed survival probabilities in the external validation cohort. The solid line represents actual nomogram performance while the dotted line represents perfect calibration.
AJCC = American Joint Committee on Cancer.

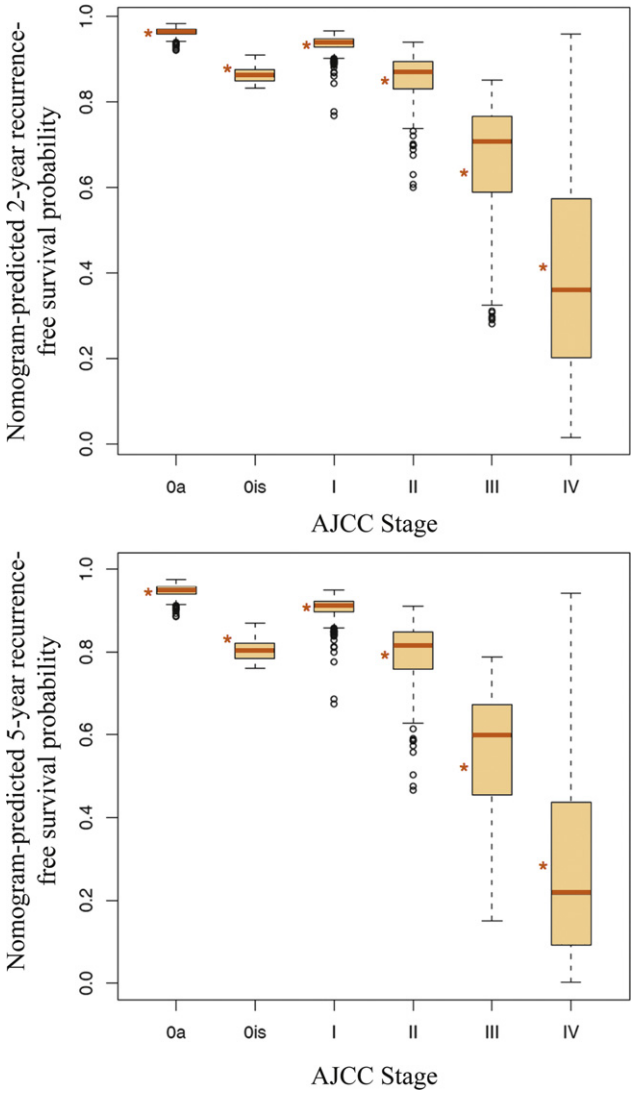

Fig. 3 – Box plots showing range of predicted recurrence-free survival (RFS) probabilities in the external validation cohort at 2 and 5 yr stratified by American Joint Committee on Cancer (AJCC) stage. The bold line indicates median, boxes represent the interquartile range (IQR), top whisker is upper quartile +1.5 × IQR, and the bottom whisker is lower quartile −1.5 × IQR. The red asterisks denote the predictions of each AJCC stage.

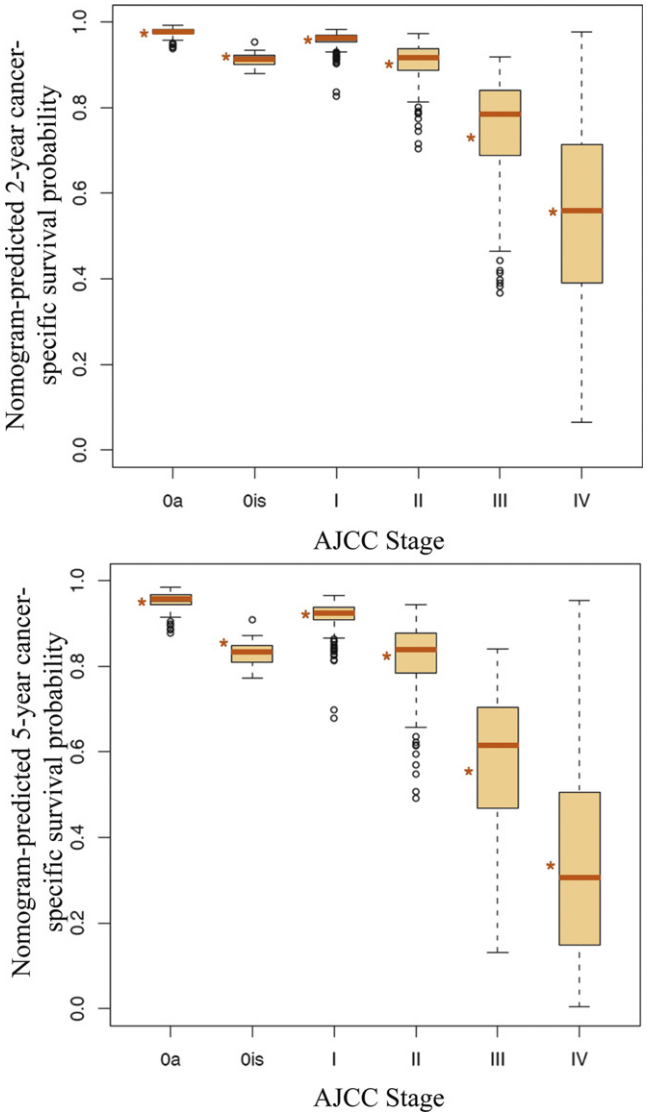

Fig. 4 – Box plots showing range of predicted cancer-specific survival (CSS) probabilities in the external validation cohort at 2 and 5 yr stratified by American Joint Committee on Cancer (AJCC) stage. The bold line indicates median, boxes represent the interquartile range (IQR), top whisker is upper quartile +1.5 × IQR, and the bottom whisker is lower quartile −1.5 × IQR. The red asterisks denote the predictions of each AJCC stage.

ranges of predicted probabilities for the 2- and 5-yr predictions of both RFS and CSS (Fig. 2).

We explored the performance of our prognostic models in relation to the AJCC staging system for UTUC [12]. In contrast to our well calibrated multivariable prognostic models, risk grouping using AJCC stage revealed a large amount of variability in predicted outcomes. Within each AJCC stage, patients had a wide range of outcomes for RFS (Fig. 3) and CSS (Fig. 4) at both 2 and 5 yr. While the predicted outcomes of patients with low-stage disease (ie, AJCC stages 0a, 0is, I) were generally uniformly good, those of patients in AJCC stages II, III, and IV were very heterogeneous. Kaplan-Meier plots of disease recurrence and CSM revealed significant overlap between AJCC stages II and III (data not shown).

4. Discussion

The outcomes of patients with UTUC after RNU are heterogeneous and, therefore, difficult to predict. Given the relative rarity of this disease, data regarding clinicopathologic predictors of outcomes were sparse until recently. Multi-institutional collaborative studies have identified several potential predictors of outcomes following RNU for UTUC, supplementing the traditional pathologic staging system [4,6,9]. In this study, we attempted to identify the strongest predictors of disease recurrence and CSM after RNU and to develop and validate a tool to facilitate clinical decision making regarding patient counseling, adjuvant therapy, and follow-up scheduling.

We confirmed that LVI and sessile tumor architecture were independently associated with disease recurrence and CSM following RNU, while tumor location was not [4,6,14,17–19]. Incorporating these pathologic variables into multivariable models enabled highly accurate prediction of RFS and CSS (c-indices: 76.8% and 81.5%, respectively). Using these multivariable models, we developed well-calibrated nomograms for the prediction of 2- and 5-yr probabilities of RFS and CSS. Jeldres et al. previously developed nomograms for prediction of CSM in patients treated with RNU using the Surveillance Epidemiology and End Results data set [2]. We confirmed the importance of the variables in their model and added LVI and tumor architecture, two strong prognostic variables that have been associated with features of biologically and clinically aggressive UTUC. The accuracies of these nomograms compare favorably to those of other prediction tools that are commonly used in medicine for clinical decision making regarding risk of cancer and need for diagnostic procedures [20,21].

We found that our nomograms were very well calibrated with minimal deviation between predicted and actual outcomes in the validation cohort. In contrast, AJCC stage grouping misclassified a large number of patients due to a very high degree of heterogeneity in outcomes within each AJCC stage, specifically for stages II, III, and IV. In addition to discrimination, calibration is a key factor for prediction. It is critical to provide accurate predictions of clinical outcomes in this cohort for appropriate patient selection regarding adjuvant therapies. Currently, only a small minority of patients with high-risk UTUC receive adjuvant chemotherapy, while a majority will die of disease [22]. Use of our accurate, well-calibrated predictive models will improve clinicians' abilities to provide evidence-based patient counseling and may be used to risk-stratify patients for follow-up scheduling and consideration for adjuvant therapies.

Several limitations of this study merit discussion, particularly those inherent to retrospective analyses. Although multiple internal and external reviews of the data set were performed, we excluded patients whose pathologic slides were not available for re-review and those without complete clinical information, thus introducing a possible selection bias. Similarly, we excluded patients in whom clear source of systemic failure was not ascertainable, such as UTUC patients who went on to develop muscle-invasive UC of the urinary bladder. The limited number of patients with UTUC, however, complicates organization of meaningful prospective randomized trials. Consequently, retrospective study design, in which rigorous clinical and pathologic review of patient data is implemented, provides a useful avenue to study patterns of failure and evaluate potential prognostic factors.

Other limitations include the fact that patients in this study underwent RNU by multiple surgeons, likely representing wide variability of surgical techniques, especially pertaining to lymphadenectomy. The impact of lymphadenectomy on clinical outcomes after RNU is an important subject for further investigation [23]. In addition, pathology slides were re-reviewed by numerous pathologists. Nevertheless, it should be noted that in our study, surgery was performed primarily by urologic oncologists at leading academic centers, and pathologists at their respective institutions evaluate a high volume of urologic cancers. While centralized pathologic review may have been preferable, results of this multi-institutional collaboration likely reflect real-world practice patterns.

5. Conclusions

We developed highly accurate prognostic models for prediction of disease recurrence and CSM following RNU. Risk stratification based upon current AJCC TNM staging suffers from significant heterogeneity within each staging group. Use of prognostic models such as ours for patients with UTUC could facilitate patient counseling and clinical decision making regarding follow-up scheduling, administration of adjuvant therapies, and evidence-based design of clinical trials. The clinical value of these tools needs to be further assessed, as has been done in bladder cancer [24].

Author contributions: Shahrokh F. Shariat had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Shariat, Margulis.
Acquisition of data: Cha, Shariat, Novara, Chromecki, Scherr, Lotan, Raman, Kassouf, Zigeuner, Remzi, Bensalah, Weizer, Kikuchi, Bolenz, Roscigno, Koppie, Ng, Fritsche, Matsumoto, Walton, Tritschler, Fajkovic, Martinez-Salamanca, Pycha, Langner, Ficarra, Patard, Montorsi, Wood, Karakiewicz, Margulis.
Analysis and interpretation of data: Cha, Shariat, Kormaksson.
Drafting of the manuscript: Cha, Shariat, Kormaksson, Margulis.
Critical revision of the manuscript for important intellectual content: Cha, Shariat, Kormaksson, Novara, Chromecki, Lotan, Raman, Zigeuner, Remzi, Roscigno, Fritsche, Ehdaie, Fajkovic, Langner, Montorsi, Margulis.
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