Prediction of Cancer Specific Survival After Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma: Development of an Optimized Postoperative Nomogram Using Decision Curve Analysis

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Abbreviations and Acronyms

CIS = carcinoma in situ
CSS = cancer specific survival
DCA = decision curve analysis
KM = Kaplan-Meier
LVI = lymphovascular invasion
RNU = radical nephroureterectomy
UTUC = upper tract urothelial carcinoma

Purpose: We conceived and proposed a unique and optimized nomogram to predict cancer specific survival after radical nephroureterectomy in patients with upper tract urothelial carcinoma by merging the 2 largest multicenter data sets reported in this population.

Materials and Methods: The international and the French national collaborative groups on upper tract urothelial carcinoma pooled data on 3,387 patients treated with radical nephroureterectomy for whom full data for nomogram development were available. The merged study population was randomly split into the development cohort (2,371) and the external validation cohort (1,016). Cox regressions were used for univariable and multivariable analyses, and to build different models. The ultimate reduced nomogram was assessed using Harrell's concordance index (c-index) and decision curve analysis.

Results: Of the 2,371 patients in the nomogram development cohort 510 (21.5%) died of upper tract urothelial carcinoma during followup. The actuarial cancer specific survival probability at 5 years was 73.7% (95% CI 71.9–75.6). Decision curve analysis revealed that the use of the best model was associated with benefit gains relative to the prediction of cancer specific survival. The optimized nomogram included only 5 variables associated with cancer specific survival on multivariable analysis, those of age ($p = 0.001$), T stage ($p < 0.001$), N stage ($p = 0.001$), architecture ($p = 0.02$) and lymphovascular invasion ($p = 0.001$). The discriminative accuracy of the nomogram was 0.8 (95% CI 0.77–0.86).

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Conclusions: Using standard pathological features obtained from the largest data set of upper tract urothelial carcinomas worldwide, we devised and validated an accurate and ultimate nomogram, superior to any single clinical variable, for predicting cancer specific survival after radical nephroureterectomy.

Key Words: ureter; kidney pelvis; carcinoma, transitional cell; survival; nomograms

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For another article on a related topic see page 1939.

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PREDICTIVE tools that enable the clinician to accurately evaluate a patient's situation are crucial for counseling objectively and for making decisions regarding the optimal treatment that results in the best possible oncologic outcome.[1] Nomograms, graphic charts that provide outcome probabilities for individual patients, are mainly used to inform patients of the likely outcomes of a treatment and have been widely used in uro-oncology.[2] A benefit of the nomogram is that it allows the integration of multiple variables and draws on the natural history of a large cohort of previously treated patients.

Due to the rarity of upper tract urothelial carcinoma,[3] clinical practice is guided by low levels of evidence and weak grades of recommendation.[4] Accurate prediction is especially difficult in UTUC where personal experience or strong clinical practice recommendations are lacking and where decisions often remain subjective. To date, the gold standard treatment of UTUC is radical nephroureterectomy, which is still proposed by urologists in the majority of cases.[5,6] RNU has provided durable local control and improved survival for decades, contingent upon respecting accepted oncologic principles such as systematic excision of the bladder cuff and attainment of negative surgical margins.[5,6] Recently 2 postoperative nomogram models for CSS after RNU were proposed by 2 large collaborative groups.[7,8] However, these 2 nomograms did not incorporate the same variables, and we believed it would be better to have a more concise, uniform model for daily urological practice than to choose between models.[7,8] Therefore, we conceived and proposed an optimized nomogram to predict CSS after RNU using the largest multi-institutional data set of UTUCs compiled to date.

MATERIALS AND METHODS

Patient Population

This was an institutional review board approved study with all of the participating sites providing the necessary institutional data sharing agreements before study initiation. Overall, 44 institutions belonging to the Upper Tract Urothelial Carcinoma Collaboration[6,7] or to the French National Database on Upper Tract Tumors[5,8] provided data about patients treated with RNU for nonmetastatic UC of the renal pelvis and/or ureter between 1987 and 2010. After combining the most updated version of the 2 collaborative data sets, reports were generated for each variable to identify data inconsistencies and other data integrity problems. Through regular communication with all sites, all identified anomalies were resolved before analysis. Overall, complete data on age, gender, tumor stage (T), nodal status (N), tumor grade, margin status, tumor architecture (papillary vs sessile), LVI, associated carcinoma in situ and tumor location (renal pelvis or ureter) were available for 3,387 patients diagnosed with UTUC. Radical surgery was performed by urologists according to the standard criteria for RNU with bladder cuff

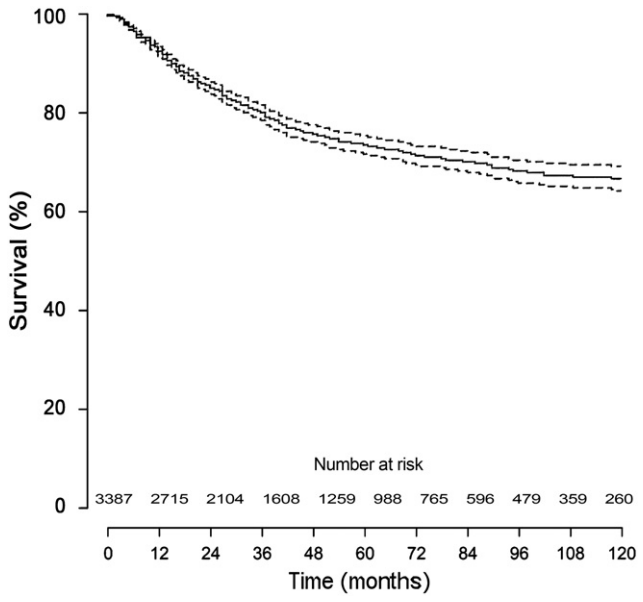

Figure 1. Kaplan-Meier plot of CSS of nomogram development cohort. Broken curves represent 95% CIs.

Table 1. *Descriptive statistics of the development and external validation cohorts*

	Nomogram Development Cohort		External Validation Cohort		Total UTUC Population		p Value
Median pt age (IQR)	69	(60.5–82.3)	69.5	(62–84)	69.3	(61–83)	0.25
No. male (%)	1,612	(68)	669	(65.8)	2,281	(67.3)	0.35
No. female (%)	759	(32)	347	(34.2)	1,106	(32.7)	
No. pathological T stage (%):							
pTa	535	(22.6)	219	(21.6)	754	(22.2)	0.37
pTis	60	(2.5)	19	(1.9)	79	(2)	
pT1	521	(22)	226	(22.2)	747	(22.1)	
pT2	410	(17.3)	182	(17.9)	592	(17.5)	
pT3	724	(30.5)	316	(31.1)	1,040	(31)	
pT4	121	(5.1)	54	(5.3)	175	(5.2)	
No. pathological N stage (%):							
pN0	676	(28.5)	286	(28.1)	962	(28.4)	0.21
pN1-3	218	(9.2)	103	(10.2)	321	(9.5)	
pNx	1,477	(62.3)	627	(61.7)	2,104	(62.1)	
No. tumor location (%):							
Renal pelvis	1,232	(52)	516	(50.8)	1,748	(51.6)	0.28
Ureter	618	(26.1)	293	(28.8)	911	(26.9)	
Both synchronously	521	(21.9)	207	(20.4)	728	(21.5)	
No. tumor architecture (%):							
Papillary	1,802	(76)	757	(74.5)	2,559	(76)	0.09
Sessile	569	(24)	259	(25.5)	828	(24)	
No. LVI (%):							
Absent	1,790	(75.5)	744	(73.2)	2,534	(75.6)	0.71
Present	581	(24.5)	272	(26.8)	853	(24.4)	
No. tumor grade (%):							
Low	427	(18)	205	(20.2)	632	(18.7)	0.48
High	1,944	(82)	811	(79.8)	2,755	(81.3)	
No. associated CIS (%)	522	(22)	177	(17.4)	699	(20.6)	0.62
No. Ca specific mortality (%)	510	(21.5)	202	(19.9)	712	(21)	0.41
Median mos followup (IQR)	42.8	(17.6–80.7)	44.2	(19.6–81.8)	43	(18.0–81.0)	—

removal, as previously described.[5,6,9] The hilar and regional lymph nodes adjacent to the ipsilateral great vessel were generally resected if palpable intraoperatively or enlarged on preoperative axial imaging. Several exclusion criteria were applied such as medical history of muscle invasive bladder UC, administration of neoadjuvant or adjuvant therapies and pT0 tumor in a definitive pathological specimen.

Followup Regimen

Patients were generally followed at 3 and 6 months postoperatively, every 6 months during the first 5 years and annually thereafter.[4] They underwent physical examination, cystoscopy, urine cytology, chest radiography and abdominopelvic computerized tomography at each visit. Disease recurrence was defined as tumor relapse in the

Table 2. *Univariable and multivariable Cox regression analyses of the association between predictor variables and CSS in the development cohort*

		Univariable Model		Multivariable Model	
		HR	p Value	HR	p Value
T stage	pTa	1.00	(referent)	1.00	(referent)
	pT1/pTis	2.52	0.01	2.27	0.001
	pT2	5.77	0.002	5.11	0.001
	pT3/4	15.2	<0.001	9.67	<0.001
N stage	pN0/x	1.00	(referent)	1.00	(referent)
	pN1/3	4.83	<0.001	2.22	0.001
LVI status	Absent vs present	3.53	<0.001	1.34	0.001
Tumor architecture	Sessile vs papillary	3.61	<0.001	1.22	0.02
Tumor grade	Low vs high	6.21	<0.001	1.79	0.01
Tumor location	Renal pelvis	1.21	(referent)	1.18	(referent)
	Ureteral	5.49	0.28	1.31	0.05
	Both	12.5	0.01	1.26	0.05
Concomitant CIS	Absent vs present	1.57	0.001	1.28	0.02
Age	Continuous	1.02	<0.001	1.02	0.001
Gender	Male vs female	0.96	0.83	—	—

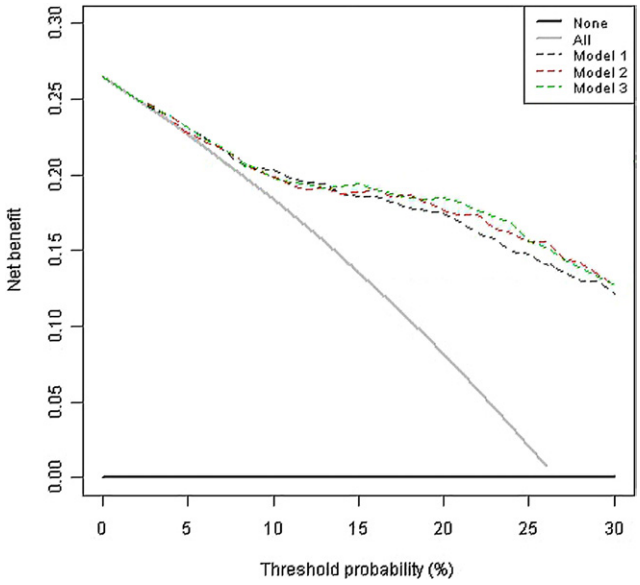

Figure 2. DCA demonstrating benefit of ultimate nomogram (model 3) compared with other models in current cohort for prediction of CSS at 5 years.

operative field, regional lymph nodes and/or distant metastasis. Cause of death was determined by the responsible clinician based on medical note review and the authorized death certificate. Only patients who had UC listed on the death certificate were considered to have died of UTUC. Perioperative deaths occurring within 30 days of surgery were censored from UTUC specific survival analyses.

Pathological Evaluation

All surgical specimens were examined by dedicated genitourinary pathologists and processed according to standardized procedures at each institution. Tumors were staged according to the 2002 TNM classification by the AJCC/UICC (American Joint Committee on Cancer/International Union Against Cancer).[10] Tumor grading was assessed according to the 1998 WHO/ISUP (International Society of Urologic Pathology) consensus.[11] Nodal status was determined by pathological assessment of retrieved lymph nodes at the time of RNU. In tumors involving the renal pelvis and ureter, the location was defined according to the site with the highest stage and/or grade.[12] Tumor architecture was defined as papillary or sessile based on the predominant feature of the index lesion.[13] LVI was defined as the presence of tumor cells within the endothelial lined space without underlying muscular walls.[14]

Statistical Analysis

Before formal analysis the database was frozen and the final data set was generated. The statistical methods consisted of the 3 steps of 1) development and internal validation of post-RNU nomograms, 2) assessment of the best model using DCA, and 3) calibration and assessment of the predictive accuracy of the ultimate nomogram in a split-sample validation cohort.

For statistical analysis actual CSS was evaluated on the entire cohort (3,387) on censored data by the Kaplan-Meier method. Cox proportional hazards regression models were used for univariable and multivariable analyses. The predictors initially analyzed included age, gender, T stage, N stage, tumor grade, associated CIS, architecture, LVI and tumor location. The whole study population was then randomly divided into 2 cohorts. The nomogram development cohort and the external validation cohort consisted of 2,371 (70% of the population) and 1,016 patients (30% of the population), respectively. We initially developed different models and chose a statistical method of training sets that prevented over-fitting. We then reused the entire data set to develop the selected models using only variables that were significantly associated with CSS. Cox regression coefficients were used to create nomograms. Using a point scale from 0 to 100, each predictive variable was weighted by assigning a point score. The point values for each variable were combined to obtain a total score, which was then correlated into the probability of 5-year CSS. A backward step-down selection process was used to generate the most informative nomograms with the smallest number of variables (ie reduced models) to avoid pollution of the model by unnecessary items.[15] Harrell's concordance index was used to quantify the discriminative accuracy of nomograms and internal validation was performed on 500 samples by the bootstrapping technique.[15–17]

For diseases with a low incidence such as UTUC, bootstrapping can improve the precision of the Kaplan-Meier survival estimate by providing a narrower CI. The c-index value only estimates the probability of concordance between predicted and observed responses. However, DCA, which was developed in recent years as a method for evaluating predictive models, visualizes the net benefit

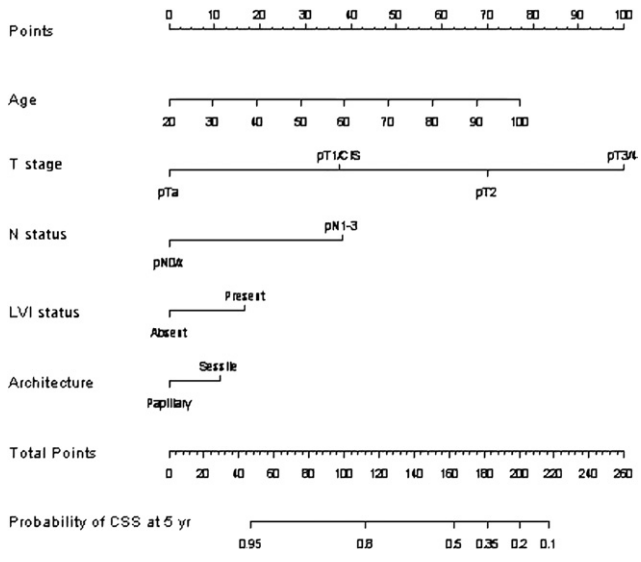

Figure 3. Proposed nomogram to predict 5-year CSS after RNU for UTUC. To calculate survival probability, patient values are identified on each axis and vertical line for each is drawn upward to Points axis. Line determines how many points each variable generates. Points for all variables are added and sum is located on Total Points line. Finally, vertical line is drawn downward from this point to identify 5-year probability of CSS.

derived from the use of a specific prediction model.[18,19] Thus, we relied on DCAs to select the best nomogram from all reduced models in the current study. Lastly, calibration plots were generated to further validate the nomogram, which was then assessed by grouping patients with respect to nomogram predicted probabilities and comparing the mean of the actual observed KM estimate of 5-year CSS in the external validation cohort. All analyses were performed with R Version 2.13.1 (R Development Core Team 2011) and the Design package,[17] with $p < 0.05$ considered significant.

RESULTS

From KM analysis the actuarial CSS probability at 5 years for the whole population (3,387) was 73.7% (95% CI 71.9–75.6, fig. 1). Table 1 presents a comparison of the relevant information for the development and validation cohorts.

Development Data Set

In the nomogram development cohort (2,371) median patient age was 69 years (IQR 60.5–82.3). Nonmuscle invasive tumor stages (Ta, Tis, T1) and muscle invasive stages (T2, T3, T4) were present in 1,116 (47.1%) and 1,255 (52.9%) patients, respectively. Low and high tumor grades were observed in 427 (18%) and 1,944 (82%) patients, respectively. Of the 37.7% of patients who underwent lymphadenectomy 676 (28.5%) and 218 (9.2%) had disease staged as N0 and N+, respectively. Concomitant CIS was identified in 522 (22%) patients. Tumors were located in the renal pelvicalyceal system, ureter, or both in 1,232 (52%), 618 (26.1%) and 521 (21.9%) patients, respectively. Overall RNU with bladder cuff removal was performed in all cases, and an open approach was used in 1,944 (82%). Of the 2,371 patients in the nomogram development cohort 510 (21.5%) died of UTUC during followup.

The predictors analyzed initially included age, gender, T stage, N stage, tumor grade, associated CIS, tumor location, tumor architecture and LVI status. The results of univariable and multivariable Cox regression analysis models are highlighted in table 2. On univariable analysis age, T stage, N stage, tumor grade, age and location, tumor architecture and LVI status were all significant predictors of CSS. When applied to a multivariable model, all variables except gender were significant. From

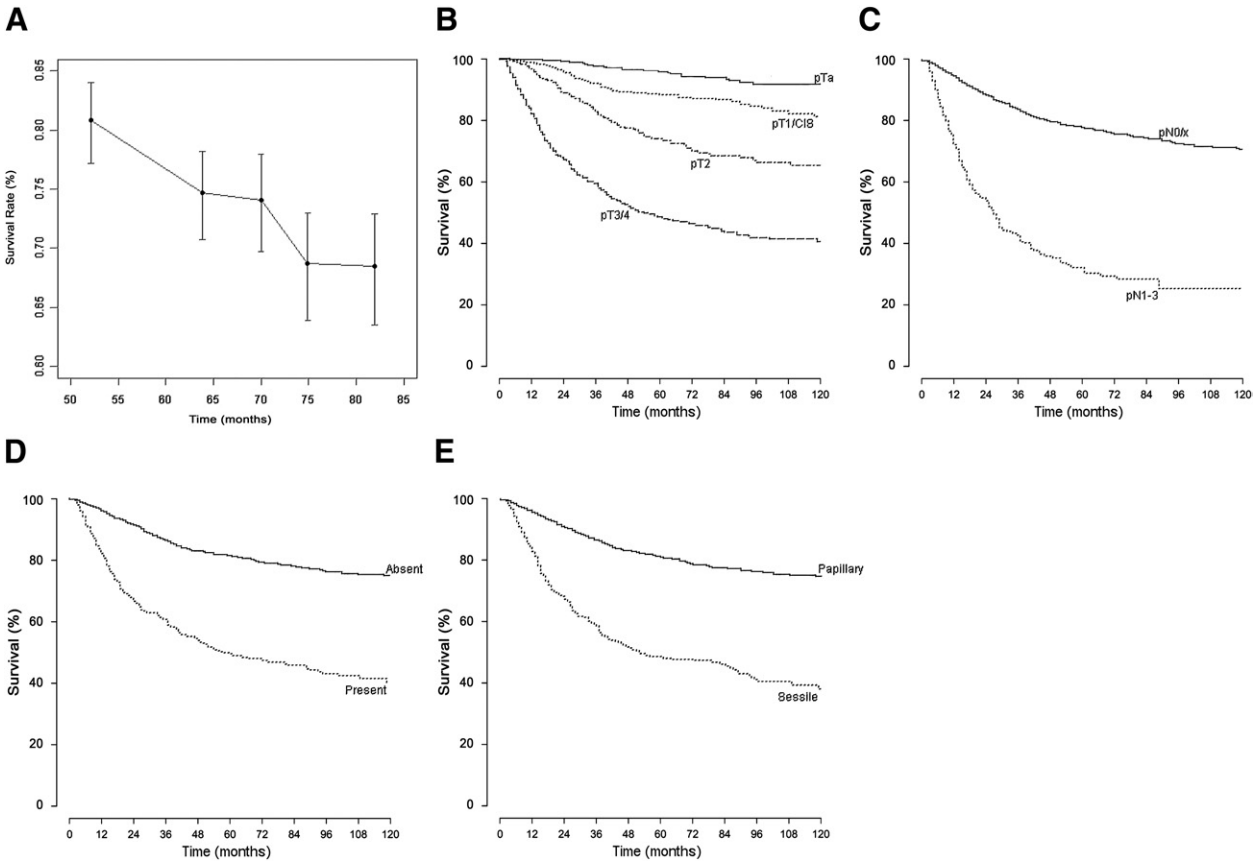

Figure 4. Kaplan-Meier plots of CSS according to 5 predictive variables included in ultimate nomogram of age (*A*), T stage (*B*), N stage (*C*), LVI status (*D*) and architecture (*E*).

this analysis the predictive accuracy was calculated and the most important univariable predictor of CSS was T stage ($p < 0.001$).

DCA revealed that the use of the best reduced model was associated with benefit gains relative to the prediction of CSS compared to other models (fig. 2). The optimized nomogram included only 5 readily available variables of age, T stage, N stage, architecture and LVI status. Our ultimate reduced nomogram is depicted in figure 3. This nomogram model had a discriminative accuracy of 0.8 (95% CI 0.77–0.86). Bootstrapping was used to internally validate the reduced model nomogram on 500 samples, which showed no deviation from the ideal. KM plots of 5-year CSS with respect to all nomograms, including predictive variables, are shown in figure 4.

Validation Data Set

Calibration plots of the nomogram predicted probabilities and the actual number surviving in the external independent cohort (1,016) are shown in figure 5. In the external validation cohort the discriminative accuracy of the model was 0.79 (95% CI 0.75–0.83).

DISCUSSION

Among prognostic models that have been developed to predict disease survival, nomograms are currently considered the most accurate paper based method to explain predicted probabilities to patients.[1,20] The clinical course of UTUC after RNU is difficult to predict because of its rarity and its highly variable natural history.[4] Due to the low incidence of UTUC, extensive experience in individual clinicians is lacking, and it is in such clinical situations that nomograms may be the most beneficial.

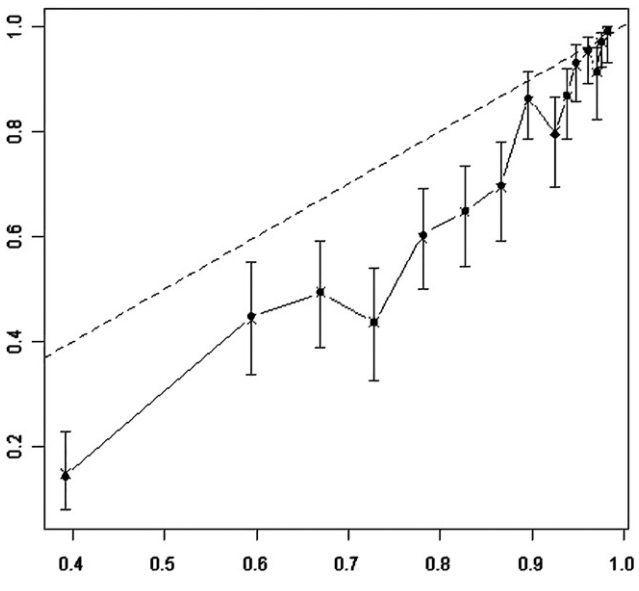

Figure 5. Calibration of nomogram. Horizontal axis (x) is nomogram predicted probability of 5-year CSS after RNU. Vertical axis (y) is actual 5-year CSS estimated with Kaplan-Meier method. Broken line in middle is reference line where ideal nomogram would lie. Solid line represents performance of nomogram. Vertical bars represent 95% CIs.

In the current study the discriminative accuracy of our optimized nomogram was 80%, which outperformed any other variable on univariable analysis. This level of discriminative accuracy is universally in line with well-known online models for prostate and renal cancer.[21,22] We used a now standardized statistical technique for nomogram development and we were able to design different predictive nomograms.[23] However, before selecting the unique and ultimate model, we decided to include DCA in the full validation process,[18,19] which guaranteed our ability to identify the most accurate model with the most informative and fewest variables.

Recently Cha[7] and Yates[8] et al proposed 2 postoperative models to predict survival after RNU in patients with UTUC. Our ultimate model is, in fact, a combination of these 2 models, but due to DCA it relies only on the efficient variables to avoid noise and pollution from other variables that are significantly associated with survival but do not improve the prediction of an outcome.[24] For instance, tumor grade is not part of the current model. However, grade is strongly correlated with the pT stage of the tumor, and the majority of UTUC cases treated with RNU are of high grade,[5,6] which makes grade nondiscriminant. Similarly a model with tumor location included as a variable had less benefit in the prediction of CSS according to DCA. The prognostic significance of tumor location in UTUC has been largely disputed over the years,[4] depending mostly on the lack of a standard definition of multifocality among groups conducting clinical research.[12,25–27]

In the current study we have proposed an optimized and a reduced nomogram that relies on 5 strong variables that were the most informative for CSS prediction, namely age, T stage, N stage, tumor architecture and LVI status. Our model is parsimonious because it relies on only 5 variables, as in the model of Yates et al.[8] However, the 2 robust variables of LVI status and tumor architecture are shared with the model of Cha et al.[7] Urologists need to request these 2 variables systematically from pathologists at the time of specimen examination.[13,14] Pathologists do not always provide LVI status to urologists, which can significantly reduce the quality of the prediction.[14]

Because nomograms can influence clinical practice,[28,29] we proposed an optimized model that could be used widely throughout the Western world. In fact, some important issues have been reported regarding the cross-cultural validation of a model. The appropriateness of applying a nomogram could de-

pend on factors related to the limited size of catchment areas and the same nomogram does not necessarily perform well in all patient populations.[30] A strategy to improve prediction and to overcome the drawbacks of a small geographic area is to assemble larger and more representative data sets. In fact, the current model is as competitive and accurate as the 2 recent models.[7,8] However, this nomogram was built by assembling the largest multi-institutional data set of UTUCs to date coming from a large area of origin (ie North America and Europe).

The multi-institutional retrospective nature of this study introduces variety in surgical techniques, pathological review and surveillance regimens. However, when it is necessary to maximize the statistical power of a study, the data are often required to be pooled, especially when the incidence of UTUC is low (3,000 new cases per year in the United States compared to 53,000 for bladder UC). Indeed, we predict CSS only and not disease recurrence as this end point is dependent on followup. Nonetheless, we believed that there was a need for a more accurate prediction model that could be applied to various patient populations, as we proposed here. Our ultimate nomogram provides the ideal format for such modeling, and its graphical presentation makes it user-friendly for clinician and patient to aid in the risk/benefit discussion of available treatments.

However, the discriminative accuracy of the nomogram did not exceed 80%. One strategy to improve the level of accuracy is to collect data prospectively, more specifically, systematically and cleanly. Such a scenario would be nearly ideal for UTUC. It is unknown how popular and widely used the available nomogram models are, and it is possible to imagine that subjective clinical decision making based on experience and guideline evidence may still prevail for common malignancies such as prostate cancer.

CONCLUSIONS

From the largest UTUC data set to date, we have proposed an accurate and ultimate nomogram, superior to any single clinical variable for predicting CSS after RNU for UTUC. This tool may help standardize and improve the prognostication of patients with UTUC.

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