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Urothelial Cancer

Pretreatment Risk Stratification for Endoscopic Kidney-sparing Surgery in Upper Tract Urothelial Carcinoma: An International Collaborative Study

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Abstract

Background: Several groups have proposed features to identify low-risk patients who may benefit from endoscopic kidney-sparing surgery in upper tract urothelial carcinoma (UTUC).
Objective: To evaluate standard risk stratification features, develop an optimal model to identify ≥pT2/N+ stage at radical nephroureterectomy (RNU), and compare it with the existing unvalidated models.
Design, setting, and participants: This was a collaborative retrospective study that included 1214 patients who underwent ureterorenoscopy with biopsy followed by RNU for nonmetastatic UTUC between 2000 and 2017.
Outcome measurements and statistical analysis: We performed multiple imputation of chained equations for missing data and multivariable logistic regression analysis with a stepwise selection algorithm to create the optimal predictive model. The area under the curve and a decision curve analysis were used to compare the models.
Results and limitations: Overall, 659 (54.3%) and 555 (45.7%) patients had ≤pT1N0/Nx and ≥pT2/N+ disease, respectively. In the multivariable logistic regression analysis of our model, age (odds ratio [OR] 1.02, 95% confidence interval [CI] 1.0–1.03, $p = 0.013$), high-grade biopsy (OR 1.81, 95% CI 1.37–2.40, $p < 0.001$), biopsy cT1+ staging (OR 3.23, 95% CI 1.93–5.41, $p < 0.001$), preoperative hydronephrosis (OR 1.37 95% CI 1.04–1.80, $p = 0.024$), tumor size (OR 1.09, 95% CI 1.01–1.17, $p = 0.029$), invasion on imaging (OR 5.10, 95% CI 3.32–7.81, $p < 0.001$), and sessile architecture (OR 2.31, 95% CI 1.58–3.36, $p < 0.001$) were significantly associated with ≥pT2/pN+ disease. Compared with the existing models, our model had the highest performance accuracy (75% vs 66–71%) and an additional clinical net reduction (four per 100 patients).
Conclusions: Our proposed risk-stratification model predicts the risk of harboring ≥pT2/N+ UTUC with reliable accuracy and a clinical net benefit outperforming the current risk-stratification models.
Patient summary: We developed a risk stratification model to better identify patients for endoscopic kidney-sparing surgery in upper tract urothelial carcinoma.

1. Introduction

Radical nephroureterectomy (RNU) with bladder cuff excision has been the gold standard for patients with upper tract urothelial carcinoma (UTUC) over the last decades [1,2]. This radical approach was primarily driven by the idea of "safety first" in a difficult-to-stage disease with potentially aggressive biology. Distal segmental ureterectomy and endoscopic laser ablation have recently been established as valid alternatives to RNU in well-selected UTUC patients [3–7]. Initially used in patients with imperative indications such as multiple comorbidities, impaired renal function, solitary kidneys, or bilateral tumors, approaches using endoscopic kidney-sparing surgery (KSS) have become an accepted curative alternative in patients with low-risk features [1].

One of the challenges in UTUC management is to accurately stage patients preoperatively because of practical and anatomic limitations [8,9]. Preoperative identification of low-risk patients who are likely to benefit from endoscopic management is essential to deliver adequate care to UTUC patients [10,11]. Several retrospective series identified preoperative tumor multifocality, architecture, hydronephrosis, tumor size, high-grade biopsy, and high-grade cytology as predictors of ≥pT2 disease [11–17] in patients who are likely to have residual microscopic disease at high risk for local and metastatic progression if managed with endoscopy. Based on such data and expert opinion [18], the European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) guidelines panels on UTUC proposed two sets of parameters (models) for pretreatment risk stratification of UTUC to support clinical decision-making [19,20]. Additionally, Margolin et al [21] published a model that integrated biopsy staging and grading. While some of these parameters have been tested individually or in different combinations, the predictive performance of the whole set of variables has not been investigated thoroughly yet. Moreover, risk stratification of neither of the EAU, the NCCN, or any other decision tool to identify candidates for endoscopic KSS has been assessed comprehensively for its clinical utility.

To address these unmet needs, we performed a large retrospective analysis to evaluate the additive predictive value of each characteristic to build the best available multivariable model for identifying ≥pT2 or lymph node–positive (pN+) staging at RNU, in order to rule out those patients who are not going to benefit from endoscopic management. Furthermore, we compared the performance accuracy and clinical benefit of our proposed model with those of other available risk stratification models.

2. Patients and methods

2.1. Study design

A study protocol was a priori elaborated and approved by the local ethics committee at the leading site (no. 1566/2017). This multi-institutional

retrospective analysis included 21 academic centers from North America, Europe, and Eastern Asia within the UTUC collaboration. All participating centers provided institutional review approval with data-sharing agreements. Each site provided a computerized database that were merged and checked for inconsistencies and integrity. Discrepancies were solved through bilateral communication. Before the analysis, the final database was created and frozen. This observational study was reported according to the STROBE statement for cohort studies and the TRIPOD statement for development and validation of prediction models [22,23].

2.2. Eligibility criteria

Overall, we collected the records of 1441 patients who underwent diagnostic ureterorenoscopy with tumor biopsy followed by RNU for UTUC between the 2000 and 2017. Patients who had evidence of metastasis (n = 9), clinically positive lymph nodes (n = 72), preoperative chemotherapy (n = 145), or bilateral synchronous tumors (n = 1) were excluded. Accordingly, 1214 patients remained for the final analysis (Fig. 1). Missing data were not part of the exclusion criteria (Supplementary Table 1).

Detailed data on EAU risk stratification parameters for UTUC, such as the biopsy grading, urine cytology, invasion on cross-sectional imaging, tumor size, preoperative hydronephrosis, previous radical cystectomy, tumor multifocality, and variant histology in biopsy material were collected. Urinary cytology was assessed from voided, instrumented, or selectively instrumented samples. The findings of urine cytology were reclassified as "negative" (negative for urothelial cell abnormality), "abnormal" (urothelial cell abnormalities including atypia, and low-grade and suspicious for high-grade urothelial carcinoma), and "high grade" (positive for high-grade urothelial carcinoma) to establish comparability across the classification systems. Invasion on imaging was defined as ≥cT3 in concordance to previous studies [11]. Magnetic resonance imaging findings were included in the analysis of cases for which computed tomography urography was not available or was contraindicated. Preoperative hydronephrosis and tumor size were also determined using these two imaging modalities. Tumor size was measured as the maximum diameter. If the tumor size was not measurable radiographically, endoscopic measurements were considered. Tumor architecture was also determined by visual inspection during ureterorenoscopy. The presence of two or more ipsilateral tumors confirmed within the same upper urinary tract unit in cross-sectional imaging or visually during ureterorenoscopy was considered multifocal.

Additionally, data on age, sex, and final pathologic stage and grade at RNU were collected. Patients who received preoperative systemic therapy were excluded due to the potential effect on the final pathologic results. RNUs were performed using open, laparoscopic, or robotic approaches according to the institution's preference. For locally advanced UTUC, the open approach was performed according to guidelines' recommendations. Although surgical modalities were not standardized among the participating centers, removing the kidney with the entire length of the ureter and bladder cuff was the standard of care at all participating centers. Bladder cuff removal was done with either the extravesical or the transvesical approach. Additional lymphadenectomy was performed in case of intraoperative suspicious lymph node involvement or at the surgeon's discretion.

2.3. Histopathologic assessment

Histopathologic examinations were performed by dedicated genitourinary pathologists at each participating center. For pathologic staging, the 2002 American Joint Committee on Cancer—International Union Against Cancer (AJCC-UICC) system was used. Tumor grade was assessed with the 2004 World Health Organization/International Society of Urological Pathology (WHO/ISUP) consensus classification.

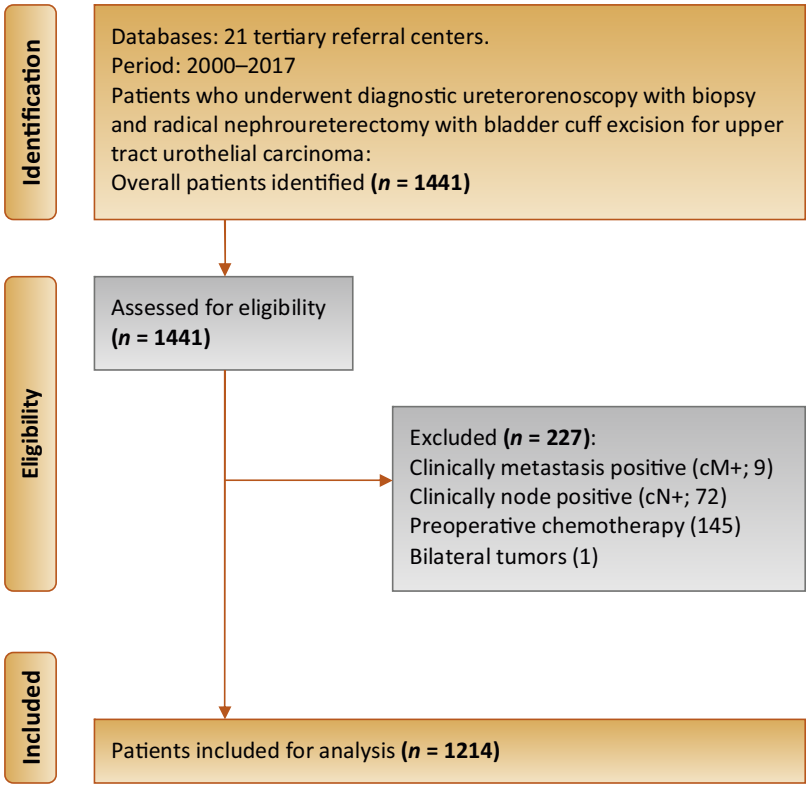

Fig. 1 – Flow diagram of patients' selection process.

2.4. Statistical analysis

Chi-square and Mann-Whitney *U* tests were used for comparison of categorical and continuous variables, respectively. All missing data (Supplementary Table 1) were assumed to be missing at random and were imputed using multiple imputation of chained equations [24]. Based on the proportion of incomplete cases, we determined that 51 imputed datasets were needed to minimize the simulation error (Monte Carlo) [25]. We performed sequential logistic regression and predictive mean matching for the imputation of binary and continuous variables, respectively. Polytomous logistic regression, or classification and regression trees were used for categorical variables. Trace plots were created to check for convergence and an adequate number of iterations (Supplementary Fig. 1–3) [26]. We used the augmented-regression approach to deal with the perfect prediction of categorical variables [27]. Rubin's rules were applied for all subsequent analyses to generate effect summaries across the imputed datasets.

Multivariable logistic regression analyses were performed to assess the risk of ≥pT2/pN+ disease. We implemented ten-fold cross validation to correct for overfit. From the overall sample size (n = 1214), the two groups containing patients with ≥pT2/pN+ and ≤pT1N0/Nx disease were randomly sampled to create ten balanced disjoin sets. The indices of the different samples in each set were gathered. From the 51 imputed datasets, the corresponding samples were extracted, which led to ten sets containing samples from each of the 51 imputed datasets.

In all ten steps of cross validation, a stepwise variable selection method based on Akaike information criterion combined with the majority method was performed to create an optimal predictive model (Supplementary Table 2). For the variables that did not appear in >50% of the cases (majority method), a Wald test was used to determine whether it should be included in the final model [25,28].

We compared the predictive accuracy and clinical net benefit of three existing models (EAU 2017, NCCN 2018, and Margolin 2018) with those of the novel model using the area under the curve receiver operating characteristics (AUC-ROC) analysis and decision curve analysis, respectively [29]. Using the variables obtained through previous steps, ten-fold cross validation was again performed, fitting ten models and pooling the estimates according to Rubin's rules. The predictions for all 51 imputed datasets were calculated separately for each set. The predictions served as input for computation of the AUC-ROC and decision curve analysis. The same procedure was implemented to obtain the performance metrics of the three existing models.

Sensitivity analyses using complete case analysis were conducted to assess the robustness of the results (Supplementary Table 3). A nomogram was created for the proposed model.

Statistical analyses were performed using STATA 16.0 (Stata Corp., College Station, TX, USA) and R statistical package v.3.6.2 (R Project for Statistical Computing, www.r-project.org). All tests were two sided, with $p < 0.05$ considered statistically significant.

3. Results

A total of 1214 patients met our inclusion criteria and were included in the analysis (Fig. 1). Table 1 summarizes the clinicopathologic features of the study population. The cohort without missing data consisted of 458 patients, which was used to perform sensitivity analyses (Supplementary Table 3). The proportions of missing data across the variables ranged from 0% to 24.3% (Supplementary Table 1).

Among 1214 ureteroscopic biopsies taken before RNU, 267 (22%) had undetermined tumor grade. Variant histology was identified in 24 (2%) of the biopsy samples. Final RNU pathology revealed 659 (54.3%) and 555 (45.7%) patients with ≤pT1N0/Nx and ≥pT2/N+ disease, respectively. Of 663 (54.6%) patients with non–muscle-invasive disease (≤pT1Nany) at RNU, 369 (55.7%) harbored pTa, 47 (7.1%) pTis, and only four (0.6%) pN+ disease. A total of 551 (45.4%) participants harbored muscle-invasive (≥pT2) disease, while 78 (14.2%) of them harbored lymph node metastases. High-grade disease was detected in 883 (72.7%) RNU specimens. Of 456 (37.6%) patients who underwent lymphadenectomy, 82 (18%) harbored lymph node metastases.

In multivariable logistic regression analyses of our proposed model, age, high-grade biopsy, biopsy cT1+ staging, preoperative hydronephrosis, tumor size, invasion on imaging, and sessile architecture were significantly

Table 1 – Characteristics of 1214 patients who underwent diagnostic ureterorenoscopy with biopsy and radical nephroureterectomy

	Pathologic TNM staging				*p* value
	≤pT1N0/Nx		≥pT2/pN+		
	No.	%	No.	%	
Age, median/IQR	70	62–76	72	64–78	<0.001
Female sex	201	30.5	202	36.4	0.030
Previous radical cystectomy	44	6.7	44	7.9	0.7
Missing	16	2.4	15	2.7	
Preoperative hydronephrosis	214	32.5	230	41.4	0.005
Missing	30	4.6	22	4.0	
Invasion on imaging (cT3+)	33	5.0	144	25.9	<0.001
Missing	65	9.9	48	8.6	
Cytology					<0.001
Negative	167	25.3	86	15.5	
Abnormal	174	26.4	155	27.9	
High grade	199	30.2	225	40.5	
Missing	119	18.1	89	16.0	
Biopsy staging					<0.001
cT0/x	182	27.6	134	24.1	
cTa	271	41.1	154	27.7	
cTis	26	3.9	15	2.7	
cT1+	36	5.5	101	18.2	
Missing	144	21.9	151	27.2	
Biopsy grading					<0.001
Gx/unclear	182	27.6	85	15.3	
Low grade	245	37.2	149	26.8	
High grade	227	34.4	311	56.0	
Missing	5	0.8	10	1.8	
Biopsy variant histology					0.026
Pure urothelial	536	81.3	443	79.8	
Squamous	4	0.6	13	2.3	
Sarcomatoid	0	0.0	4	0.7	
Glandular	0	0.0	1	0.2	
Others	1	0.2	1	0.2	
Missing	118	17.9	93	16.8	
Sessile architecture	71	10.8	143	25.8	<0.001
Missing	106	16.1	126	22.7	
Tumor size (cm)					<0.001
≤1	120	18.2	65	11.7	
1.1–2	184	27.9	123	22.2	
2.1–3	113	17.1	106	19.1	
>3	146	22.2	165	29.7	
Missing	96	14.6	96	17.3	
Multifocality	156	23.7	132	23.8	0.9
Missing	32	4.9	25	4.5	
Total	659	54.3	555	45.7	

IQR = interquartile range; TNM = tumor, node, metastasis.

associated with ≥pT2/pN+ disease (Table 2). Within the 2017 EAU guidelines' risk stratification model, tumor size >2 cm was significantly associated with ≥pT2/pN+ (odds ratio [OR] 1.38, 95% confidence interval [CI] 1.04–1.83, p = 0.024), while variant histology on biopsy was not (OR 1.29, 95% CI 0.49–3.42, p = 0.6). The tumor size cutoff >1.5 cm in the NCCN 2018 model was also significantly associated with ≥pT2/pN+ (OR 1.51, 95% CI 1.04–2.18, p = 0.032). Our proposed model had the highest bias-corrected performance accuracy (ie, 75% AUC-ROC), higher than that of the three unvalidated models (EAU 2017, NCCN 2018, and Margolin 2018 ranging between 66% and 71%; Table 2) based on internal validation.

Using decision curve analysis, our proposed model outperformed the other models in terms of clinical net benefit (Fig. 2A) and net reduction (Fig. 2B), specifically within the crucial threshold probability of 20–40%. Within this range of threshold probabilities, the EAU 2017 and NCCN 2018 risk stratification models had similar performance to each other, with minimal advantage for the EAU 2017 model. At a threshold probability of 30%, RNU could be avoided in four of 100 additional patients by using our proposed model compared with the EAU 2017 model. Absolute and relative numbers, bias corrected by internal validation and stratified by threshold probability, are presented in Table 3 comparing the proposed model with the EAU model. The nomogram of the proposed model is presented in Figure 3.

4. Discussion

Our analysis confirmed the predictive value of most established pretreatment risk stratification parameters in identifying patients with ≥pT2 or lymph node–positive disease at RNU. We identified the risk factors with the best performance in a stepwise fashion and created the best available predictive model for clinical practice. The proposed risk stratification estimates ≥pT2/N+ UTUC with higher accuracy than the EAU or NCCN guidelines' risk stratification models.

Our data have confirmed the suggested predictive performance of age, biopsy grading, biopsy cT1+ staging, preoperative hydronephrosis, tumor size, invasion on imaging (cT3+), and sessile architecture with statistical significance. On the contrary, the additive value of previous radical cystectomy, cTa/cTis biopsy staging, and tumor multifocality [14] appears to be limited; this can be appreciated by inspecting our nomogram based on the proposed risk stratification model.

The decision curve analysis demonstrated that the EAU model performed marginally better than the NCCN risk stratification model among the clinically important risk thresholds between 20% and 40%. However, our proposed model revealed significant differences in discrimination accuracy, clinical net benefit, and net reduction compared with both the EAU and the NCCN model. Using our risk stratification model between the threshold probability of 20% and 40%, up to four per 100 additional patients could avoid unnecessary RNU. The major difference between our model and the EAU model is the inclusion of biopsy staging and tumor architecture. These two parameters were robust predictors in multivariable logistic regression analyses. Margolin et al [21] found that cT1+ biopsy staging is a powerful predictor for muscle-invasive UTUC with an OR of 9.0. Margolin et al's [21] model comprised only three parameters (biopsy cT1+ staging, biopsy grading, and age),

Table 2 – Multivariable logistic regression models pooled across multiple imputations for predicting ≥pT2/pN+ disease in patients undergoing radical nephroureterectomy

	Proposed model		EAU 2017		NCCN 2018		Margolin 2018	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Age	1.02 (1.00–1.03)	0.013	–	–	–	–	1.02 (1.01–1.03)	0.001
Female sex	1.28 (0.97–1.68)	0.079	–	–	–	–	–	–
Previous radical cystectomy	0.96 (0.58–1.57)	0.9	0.97 (0.60–1.56)	0.9	–	–	–	–
High-grade biopsy	1.81 (1.37–2.40)	<0.001	2.12 (1.62–2.76)	<0.001	2.07 (1.60–2.68)	<0.001	2.34 (1.84–2.97)	<0.001
Biopsy staging			–	–	–	–		
cT0/x	Ref.							
cTa	0.91 (0.67–1.24)	0.5					Ref.	
cTis	0.55 (0.25–1.18)	0.13					Ref.	
cT1+	3.23 (1.93–5.41)	<0.001					3.22 (2.00–5.19)	<0.001
Biopsy variant histology	–	–	1.29 (0.49–3.42)	0.6	–	–	–	–
High-grade cytology	1.32 (0.97–1.79)	0.078	1.38 (1.03–1.83)	0.029	–	–	–	–
Preoperative hydronephrosis	1.37 (1.04–1.80)	0.024	1.35 (1.04–1.75)	0.024	–	–	–	–
Tumor size	1.09 (1.01–1.17) [a]	0.029	1.38 (1.04–1.83) [b]	0.024	1.51 (1.04–2.18) [c]	0.032	–	–
Invasion on imaging (cT3+)	5.10 (3.32–7.81)	<0.001	5.62 (3.74–8.44)	<0.001	4.95 (3.29–7.46)	<0.001	–	–
Multifocality	0.74 (0.54–1.01)	0.061	0.82 (0.61–1.10)	0.19	0.80 (0.60–1.08)	0.15	–	–
Sessile architecture	2.31 (1.58–3.36)	<0.001	–	–	2.47 (1.73–3.52)	<0.001	–	–
AUC-ROC (95% CI)	75% (74.6–74.9%)		71% (70.9–71.1%)		71% (71.2–71.5%)		66% (66.3–66.5%)	

AUC-ROC = area under the curve receiver operating characteristics; CI = confidence interval; EAU = European Association of Urology; NCCN = National Comprehensive Cancer Network; OR = odds ratio; Ref. = reference.

[a] Tumor size as a continuous variable.

[b] Tumor size >2 cm.

[c] Tumor size ≥1.5 cm.

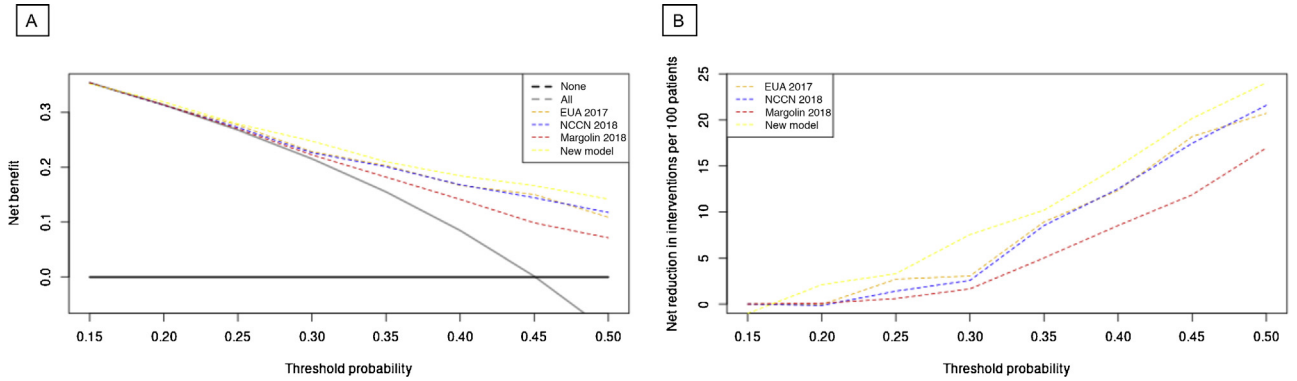

Fig. 2 – Decision curve analyses comparing different models demonstrating the (A) clinical net benefit and (B) net reduction associated with its use. Clinical net benefit of 0.05 is interpreted as identifying additional five of 100 patients with ≥pT2/pN+ disease compared with using no auxiliary model. A clinical net reduction in interventions of 4 means that the respective model can identify four of 100 patients with <pT2 disease in whom RNU can be avoided. The threshold probability resembles the predicted risk of ≥pT2/pN+ disease. EAU = European Association of Urology; NCCN = National Comprehensive Cancer Network; RNU = radical nephroureterectomy.

Table 3 – Clinical net benefit and net reduction by the proposed risk stratification model in comparison to the EAU 2017 model

Threshold probability (%)	Absolute net benefit	Net benefit vs treating all	Net benefit vs EAU 2017	Net reduction vs treating all	Net reduction vs EAU 2017
15	0.35	0	0	0	0
20	0.32	0.01	0	2	2
25	0.28	0.01	0	3	1
30	0.25	0.03	0.02	8	4
35	0.21	0.05	0.01	10	1
40	0.18	0.10	0.02	15	3
45	0.17	0.17	0.02	20	2
50	0.14	0.24	0.03	24	3

EAU = European Association of Urology; RNU = radical nephroureterectomy.
Clinical net benefit of 0.05 is interpreted as identifying additional five of 100 patients with ≥pT2/pN+ disease compared with using no auxiliary model. A clinical net reduction in interventions of 4 means that the respective model can identify four of 100 patients with <pT2 disease in whom RNU can be avoided. The threshold probability resembles the predicted risk of ≥pT2/pN+ disease.

although the AUC-ROC was 66%. This result emphasizes the predictive value of high-grade biopsy and cT1+ staging for estimating the risk for advanced UTUC. Tumor architecture appears to be another important risk factor [15]. In the NCCN model, tumor architecture compensated for other important risk factors that were not included as compared with the EAU model. Only pathologic architecture after RNU has widely been investigated [15]. Two other preoperative nomograms predicting pathologic and recurrence outcomes after RNU have also found tumor architecture to be a robust preoperative factor as defined by diagnostic ureterorenoscopy [30,31].

We found that invasion on imaging (cT3+) was the most decisive factor predicting ≥pT2 and/or lymph node–positive disease. Similarly, a single-center retrospective study [11] showed that invasion in cross-sectional imaging predicted ≥pT2 stage with an OR of 4.1, but had limited discriminative ability (AUC-ROC), which was 58%. Several investigators reported that variant histology at RNU specimen was associated with advanced tumor stage; variant histology using biopsy did not retain such an association. This finding can be explained by the low yield of ureteroscopic biopsy and the limitations of our database. The inclusion of this feature in the EAU risk stratification for UTUC was based on expert opinion guided by its prognostic value at RNU specimen [32,33] and bladder cancer literature [34]. In fact, this analysis, up to our knowledge, is the first to evaluate variant histology within biopsy material and its association with advance pathologic stage. Variant histology as well as tumor grade is not diagnosed easily using ureteroscopic biopsy [35]. This is evident by the low rate of variant histology and high rate of undetermined tumor grade [36] in our study as compared with contemporary RNU series [33].

Although, invasion on imaging [11] and biopsy cT1+ staging were highly significant in logistic regression analyses, their clinical net benefit in decision curve analysis within the threshold probability of 20–40% was limited. This is where treatment decisions regarding KSS are difficult and where a predictive model might help physicians in patient counseling and treatment planning. Our nomogram shows that the more points a risk factor achieves, the less relevant it is in the smaller threshold probabilities. By contrast, we found that biopsy grading and urine cytology added significant predictive value to the models' 20–40% threshold zone despite being statistically insignificant in

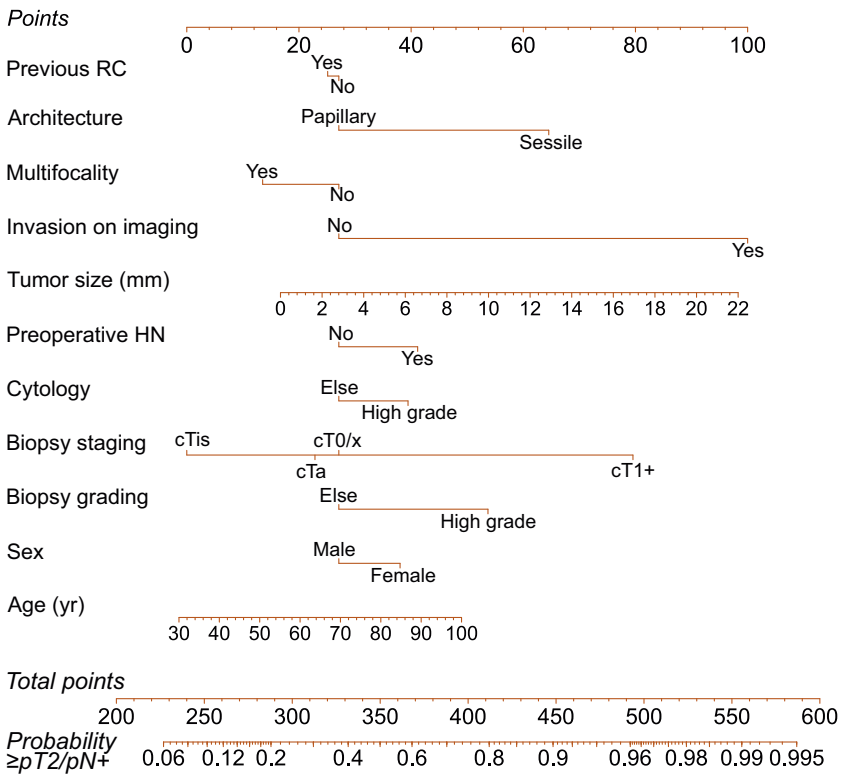

Fig. 3 – Nomogram predicting the probability of ≥pT2/pN+ disease in patients undergoing radical nephroureterectomy. Instructions: Locate the patient's age on the corresponding axis. Draw a line straight upward to the point axis to determine the points toward the probability of ≥pT2/pN+ disease the patient receives for his age value. Perform this process for each additional variable and sum the points for each predictor. Locate the final sum on the total point axis. Draw a line straight down to find the patient's probability of having ≥pT2/pN+ disease. HN = hydronephrosis; RC = radical cystectomy.

the multivariable model. Several studies have shown that these two parameters are important for treatment decision-making [11–13].

Similar to previous reports [37–39], we found that preoperative hydronephrosis and tumor size were significantly associated with a high risk of ≥pT2N0/Nx or pN+. Surprisingly, the >1.5 cm cutoff of the NCCN guidelines was a stronger predictor for ≥pT2/pN+ disease than the new EAU tumor size cutoff of >2 cm [17,19,20]. However, the statistical difference was small and probably depended on the interaction with other factors in the multivariable models. Our results revealed that tumor size performed best as a continuous variable and can be clinically meaningful by inclusion into a nomogram. However, this is only of minor benefit as there is a significant need to improve UTUC risk stratification, especially in the threshold probability area of 10–30%; this is likely to be fruitful only through identification and validation of robust biomarkers [40–42]. Additionally, tumor size has important practical implications for endoscopic management especially.

Here, we acknowledge the limitations and strengths of our study. This retrospective collaborative analysis represents a well-selected cohort of UTUC patients and inherent selection bias, among other limitations, which might affect our results. Particularly, these patients underwent RNU and may have had factors preventing KSS, whereas those with more favorable features were likely not a part of this database, given that the database spanned over a long period of time (2000–2017) where endoscopic KSS was not commonly performed. The data show that there may have been additional patients who could have been candidates for endoscopic management had they accepted the possible higher local recurrence risks. Furthermore, we cannot rule out that selected patients received ureteroscopic laser ablation during initial diagnostic ureterorenoscopy.

We tried to minimize these limitations by performing multiple imputation for missing values assuming that the missing data were missing at random (MAR). By doing so, we reduced selection bias by including all identified patients and allowed the inclusion of many UTUC risk stratification parameters into the models. Nevertheless, the MAR assumption is not devoid of inconsistencies with the potential of introducing a bias. Furthermore, we made our predefined selection process transparent by a flow diagram (Fig. 1) and strengthened the reporting according to the STROBE guidelines for observational cohort studies [22]. We acknowledge the lack of a central pathology review of biopsies and RNU specimens. Nevertheless, all involved institutions within the UTUC collaboration are academic centers with dedicated uropathologists who have expertise in this disease. No laboratory parameters, such as hemoglobin, DeRitis ratio, serum sodium, and neutrophil-lymphocyte ratio, which

have been shown to be predictive in other studies, were evaluated, which could have affected the nomogram interactions. Additionally, there was no central review of cross-sectional imaging to define invasion (cT3+) and tumor size. Such limitations can be addressed in future well-designed prospective studies to determine the most optimal model for decision-making and patient counseling.

5. Conclusions

Invasion on imaging, biopsy cT1+ staging, endoscopic-based sessile tumor architecture, and high-grade biopsy are the strongest predictors of the likelihood of harboring muscle-invasive or lymph node–positive disease, allowing for exclusion of patients from endoscopic management. Notably, biopsy grading and urine cytology perform best when the probability for invasive or lymph node–positive UTUC is between 20% and 40%. The predictive values of previous radical cystectomy and tumor multifocality are limited. The novel proposed risk stratification estimates the risk of harboring ≥pT2N0/Nx or pN+ disease with higher discrimination accuracy and clinical net benefit. Our model, which outperforms the current guidelines' risk stratification models, is likely to help improve the decision-making process for endoscopic KSS. External validation, robust predictive biomarkers, and more accurate decision tools are urgently needed to better identify the patients who are likely to benefit from ureteroscopic management.

***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.

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Acquisition of data: Foerster, Matin, Petros, Azizi, Gupta, Li, Seisen, Clinton, Mir, Schweitzer, Mari, Kimura, Bandini, Mathieu, Ku, Marcq, Guruli, Grabbert, Czech, Muilwijk, D'Andrea, Soria, Graffeille, Moschini.
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Critical revision of the manuscript for important intellectual content: Matin, Azizi, Gupta, Li, Seisen, Clinton, Xylinas, Mir, Schweitzer, Mari, Kimura, Bandini, Mathieu, Ku, Marcq, Guruli, Grabbert, Czech, Muilwijk, Pycha, D'Andrea, Petros, Spiess, Bivalacqua, Wu, Rouprêt, Krabbe, Hendricksen, Egawa, Briganti, Moschini, Graffeille, Kassouf, Autorino, Heidenreich, Chlosta, Joniau, Soria, Pierorazio.
Statistical analysis: Foerster, Abufaraj, Kimura, D'Andrea, Soria.
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Supervision: Matin, Li, Seisen, Xylinas, Mir, Mathieu, Ku, Pycha, Petros, Spiess, Bivalacqua, Wu, Rouprêt, Krabbe, Hendricksen, Egawa, Briganti, Kassouf, Autorino, Heidenreich, Chlosta, Joniau, Pierorazio, Shariat.
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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2021.05.004.

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