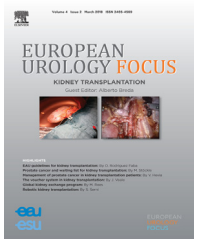
available at www.sciencedirect.com
journal homepage: www.europeanurology.com/eufocus



Urothelial Cancer

Accuracy and Clinical Utility of a Tumor Grade- and Stage-based Predictive Model in Localized Upper Tract Urothelial Carcinoma

Satoshi Katayama [a,b], *Keiichiro Mori* [a,c], *Victor M. Schuettfort* [a,d], *Benjamin Pradere* [a,e], *Hadi Mostafaei* [a,f], *Fahad Quhal* [a,g], *Pawel Rajwa* [a,h], *Reza Sari Motlagh* [a,i], *Ekaterina Laukhtina* [a,j], *Marco Moschini* [a,k], *Nico C. Grossmann* [a,l], *Motoo Araki* [b], *Jeremy Yuen-Chun Teoh* [m], *Morgan Rouprêt* [n], *Vitaly Margulis* [o], *Dmitry Enikeev* [j], *Pierre I. Karakiewicz* [p], *Mohammad Abufaraj* [a,q], *Eva Compérat* [a], *Yasutomo Nasu* [b], *Shahrokh F. Shariat* [a,j,o,q,r,s,t,u,*]

[a] *Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria;* [b] *Department of Urology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan;* [c] *Department of Urology, The Jikei University School of Medicine, Tokyo, Japan;* [d] *Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany;* [e] *Department of Urology, University Hospital of Tours, Tours, France;* [f] *Research Center for Evidence Based Medicine, Tabriz University of Medical Sciences, Tabriz, Iran;* [g] *Department of Urology, King Fahad Specialist Hospital, Dammam, Saudi Arabia;* [h] *Department of Urology, Medical University of Silesia, Zabrze, Poland;* [i] *Men's Health and Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran;* [j] *Institute for Urology and Reproductive Health, Sechenov University, Moscow, Russia;* [k] *Department of Urology, Luzerner Kantonsspital, Luzern, Switzerland;* [l] *Department of Urology, University Hospital Zurich, Zurich, Switzerland;* [m] *S.H. Ho Urology Centre, Department of Surgery, The Chinese University of Hong Kong, Hong Kong SAR, China;* [n] *GRC 5 Predictive Onco-Uro, Urology, Sorbonne University, Pitie-Salpetriere Hospital, Paris, France;* [o] *Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX, USA;* [p] *Cancer Prognostics and Health Outcomes Unit, University of Montreal Health Centre, Montreal, Canada;* [q] *Research Division of Urology, Department of Special Surgery, The University of Jordan, Amman, Jordan;* [r] *Department of Urology, Weill Cornell Medical College, New York, NY, USA;* [s] *Department of Urology, Second Faculty of Medicine, Charles University, Prague, Czech Republic;* [t] *Karl Landsteiner Institute of Urology and Andrology, Vienna, Austria;* [u] *European Association of Urology Research Foundation, Arnhem, The Netherlands*

Article info

Article history:
Accepted May 12, 2021

Associate Editor: Richard Lee

Keywords:
Upper tract urothelial carcinoma
Conservative treatment
Kidney-sparing surgery
Predictive model
Low-grade tumor

Abstract

Background: Among various clinicopathologic factors used to identify low-risk upper tract urothelial carcinoma (UTUC), tumor grade and stage are of utmost importance. The clinical value added by inclusion of other risk factors remains unproven.
Objective: To assess the performance of a tumor grade- and stage-based (GS) model to identify patients with UTUC for whom kidney-sparing surgery (KSS) could be attempted.
Design, setting, and participants: In this international study, we reviewed the medical records of 1240 patients with UTUC who underwent radical nephroureterectomy. Complete data needed for risk stratification according to the European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) guidelines were available for 560 patients.
Outcome measurements and statistical analysis: Univariable and multivariable logistic regression analyses were performed to determine if risk factors were associated with the presence of localized UTUC. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the GS, EAU, and NCCN models in predicting pathologic stage were calculated.

* Corresponding author. Department of Urology, Comprehensive Cancer Center, Vienna General Hospital, Medical University of Vienna, Währinger Gürtel 18–20, 1090 Vienna, Austria.
Tel. +43 1 4040026150; Fax: +43 14040023320.
E-mail address: shahrokh.shariat@meduniwien.ac.at (S.F. Shariat).

https://doi.org/10.1016/j.euf.2021.05.002

Please cite this article in press as: Katayama S, et al. Accuracy and Clinical Utility of a Tumor Grade- and Stage-based Predictive Model in Localized Upper Tract Urothelial Carcinoma. Eur Urol Focus (2021), https://doi.org/10.1016/j.euf.2021.05.002

Results and limitations: Overall, 198 patients (35%) had clinically low-grade, noninvasive tumors, and 283 (51%) had ≤pT1disease. On multivariable analyses, none of the EAU and NCCN risk factors were associated with the presence of non–muscle-invasive UTUC among patients with low-grade and low-stage UTUC. The GS model exhibited the highest accuracy, sensitivity, and negative predictive value among all three models. According to the GS, EAU, and NCCN models, the proportion of patients eligible for KSS was 35%, 6%, and 4%, respectively. Decision curve analysis revealed that the net benefit of the three models was similar within the clinically reasonable range of probability thresholds.

Conclusions: The GS model showed favorable predictive accuracy and identified a greater number of KSS-eligible patients than the EAU and NCCN models. A decision-making algorithm that weighs the benefits of avoiding unnecessary kidney loss against the risk of undertreatment in case of advanced carcinoma is necessary for individualized treatment for UTUC patients.

Patient summary: We assessed the ability of three models to predict low-grade, low-stage disease in patients with cancer of the upper urinary tract. No risk factors other than grade assessed on biopsy and stage assessed from scans were associated with better prediction of localized cancer. A model based on grade and stage may help to identify patients who could benefit from kidney-sparing treatment of their cancer.

1. Introduction

Radical nephroureterectomy (RNU) with bladder cuff excision (with or without lymphadenectomy) remains the standard of care for patients with high-risk nonmetastatic upper tract urothelial carcinoma (UTUC) [1–4]. Kidney-sparing surgery (KSS), including segmental ureterectomy and endoscopic ablation, has been discussed as an alternative treatment option for three decades. However, the development of an accurate preoperative staging method for UTUC is crucial to expanding the indication for KSS so that all patients who could potentially benefit from KSS have the chance to do so [5]. To overcome the limitation of inaccurate preoperative staging, the current guidelines recommend a risk stratification strategy for decision-making and patient counseling that combines previously identified risk factors [3,6]. Several preoperative models have successfully validated the utility of strategies that consider a combination of these risk factors [7,8]. Nevertheless, according to the National Cancer Data Base, fewer than 20% of patients with low-grade UTUC receive endoscopic treatment [9], indicating that the current criteria for KSS might be too stringent. Brien et al [10] were the first to provide a predictive model with remarkable accuracy; they found that three variables (presence of hydronephrosis, tumor grade on biopsy, and urinary cytology findings) provided a negative predictive value of 100% for muscle-invasive or non–organ-confined UTUC. However, in their study, only 8% of patients met these criteria at the cost of pursuing the predictive accuracy, and many remaining patients are likely to have received overtreatment. Therefore, optimization of the current risk stratification strategy without comprising oncologic safety is needed to identify the sweet spot between over- and under-treatment.

The best-established independent risk factors are ureteroscopy (URS)-based tumor grade and clinical imaging-based tumor stage [11]. Tumors presumed to be low-grade and low-stage UTUC have been managed successfully using KSS [12]. For clinically low-grade, low-stage tumors, other risk factors limit the adoption of KSS, but the value that they add in risk prediction remains unproven in well-designed validation studies. Thus, we sought to evaluate the clinical value of each risk factor in a group of patients presumed to have low-grade, low-stage UTUC in order to refine the selection of patients well suited to undergo KSS.

2. Patients and methods

2.1. Eligible patients

This multicenter retrospective analysis was approved by the institutional review boards of all participating institutions. We retrospectively reviewed the medical charts of 1240 patients with clinically nonmetastatic UTUC who underwent URS biopsies followed by RNU between 2000 and 2016 at 16 academic centers in Europe, North America, and Eastern Asia. Computerized data sets were generated for merging. Through regular communication with all institutions, all discrepancies identified were resolved before the final data set was produced for the current analysis. RNU was performed using an open or laparoscopic approach, with distal ureter management at the surgeon's discretion. Bladder cuff excision was performed via an extravesical or transvesical approach [4]. Lymphadenectomy was also performed at the surgeon's discretion; extended lymphadenectomy was not routinely performed [13]. Patients who received neoadjuvant chemotherapy for UC, those who underwent conservative treatment, and those for whom we could not determine tumor grade using URS were excluded from the analyses. Based on the guidelines' risk classifications, only patients with complete data were included in this analysis.

2.2. Predictive models

We compared the ability of three models to predicting the presence of histologically confirmed localized UTUC (≤pT1 and the absence of lymph node metastasis in the final RNU pathology specimen): a tumor grade- and stage-based (GS) model comprising tumor grade determined on URS and invasiveness assessed via computed tomography urography (CTU) or

Please cite this article in press as: Katayama S, et al. Accuracy and Clinical Utility of a Tumor Grade- and Stage-based Predictive Model in Localized Upper Tract Urothelial Carcinoma. Eur Urol Focus (2021), https://doi.org/10.1016/j.euf.2021.05.002

Table 1 – Factors for classification of upper tract urothelial carcinoma risk in each model

Risk factor	GS model	EAU model	NCCN model
Tumor stage	✓	✓	✓
Tumor grade	✓	✓	✓
Hydronephrosis		✓	
Tumor size [a]		✓	✓
Urinary cytology		✓	✓
Multifocality		✓	✓
Variant histology		✓	
Previous radical cystectomy		✓	
Tumor architecture [b]			✓

GS = tumor grade- and stage-based model; EAU = European Association of Urology; NCCN = National Comprehensive Cancer Network.
[a] Cutoff for tumor size is 2 cm in the EAU guidelines and 1.5 cm in the NCCN guidelines.
[b] Flat/sessile versus papillary architecture.

magnetic resonance imaging (MRI); the European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) models were based on the risk factors recommended by each guideline (Table 1).

2.3. Variable evaluation

Tumor grading was according to the 2004 World Health Organization/International Society of Urological Pathology consensus classification. Tumor staging was based on the 2002 American Joint Committee on Cancer-International Union Against Cancer system. All cases were re-evaluated based on criteria agreed between pathologists of the UTUC collaboration. For cases before 2002 and 2004, restaging and regrading were performed. On the basis of urinary cytology findings, tumors were classified as high grade or not high grade; cases of atypical urinary cytology that were not clearly classified as high grade, were classified as not high grade. Tumor size was pathologically measured and used to divide tumors into two categories as the size-based definition of high risk varies between the EAU (>2 cm) and NCCN (>1.5 cm) guidelines.

2.4. Statistical analysis

The analyses were performed for the group of patients with low-grade (on URS) and low-stage (on CTU/MRI) UTUC. After adjustments for other risk factors, univariable and multivariable logistic regression analyses were performed to determine whether a particular risk factor was associated with the presence of pathologically localized UTUC. The sensitivity, specificity, positive predictive value (PPV), negative predictive value, and accuracy of the models in predicting the final pathologic stage were calculated. The area under the receiver operating characteristic curve (AUC) was calculated to assess the accuracy of each predictive model. We applied decision curve analysis (DCA) to evaluate the net benefit of the models in decision-making with the clinically relevant range of probability thresholds. The classification and regression tree (CART) method, a decision tree model, was also used to develop an algorithm. Each root node included PPV and was bifurcated by repeatedly using the Gini coefficient, eventually resulting in terminal nodes. Statistical analyses were performed using STATA v14.0 (Stata Corp., College Station, TX, USA) and R v3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). Two-sided p values <0.05 were defined as statistically significant.

3. Results

Complete data on EAU risk factors were available for 745 patients, among whom tumor grade via pathologic evaluation on URS was not determinable in 185. These patients were excluded, leaving a total of 560 patients for analysis. The clinical and pathologic characteristics of the cohort are described in Table 2. In total, 283 patients (51%) had ≤pT1 disease and 277 (49%) had ≥pT2 according to

Table 2 – Clinical and pathologic characteristics of all patients and patient with clinically LG, noninvasive UTUC [a]

	All patients	LG, noninvasive UTUC
Patients, *n* (%)	560 (100)	198 (100)
Median age, yr (interquartile range)	71 (64–77)	70 (62–76)
Sex, *n* (%)		
Male	349 (62)	126 (64)
Female	211 (38)	72 (36)
Invasiveness on CTU/MRI		
Yes	134 (24)	
No	426 (76)	
Biopsy grade, *n* (%)		
Low grade	233 (42)	
High grade	327 (58)	
Hydronephrosis, *n* (%)		
Yes	209 (37)	68 (34)
No	351 (63)	130 (66)
High-grade cytology, *n* (%)		
Yes	229 (41)	46 (23)
No	331 (59)	152 (77)
Tumor size, *n* (%)		
≤2 cm	266 (47)	100 (51)
>2 cm	294 (53)	98 (49)
Multifocality, *n* (%)		
Yes	149 (27)	35 (18)
No	411 (73)	163 (82)
Histological variant, *n* (%)		
Yes	16 (3)	5 (3)
No	544 (97)	193 (97)
Tumor location, *n* (%)		
Renal pelvis	164 (29)	74 (37)
Ureter	251 (45)	75 (38)
Data missing	145 (26)	49 (25)
Previous radical cystectomy		
Yes	34 (6)	3 (2)
No	526 (94)	195 (98)
Tumor architecture, *n* (%)		
Papillary	379 (68)	159 (80)
Sessile	131 (23)	20 (10)
Missing	50 (9)	19 (10)
Pathologic grade, *n* (%)		
Low grade	122 (22)	90 (45)
High grade	430 (77)	108 (55)
Grade unknown	8 (1)	0 (0)
Pathologic stage, *n* (%)		
T0/Tx	9 (2)	4 (2)
Ta	164 (29)	92 (46)
Tis	15 (3)	3 (1)
T1	95 (17)	40 (20)
T2	104 (18)	31 (16)
T3	157 (28)	27 (14)
T4	16 (3)	1 (1)
Lymph node status, *n* (%)		
pNx	375 (67)	50 (25)
pN0	151 (27)	145 (73)
pN1	19 (3)	0 (0)
pN2–3	15 (3)	3 (2)

LG = low grade; UTUC = upper tract urothelial carcinoma; CTU = computed tomography urography; MRI = magnetic resonance imaging.
[a] Low grade observed on ureteroscopy and noninvasive nature observed on CTU/MRI.

Please cite this article in press as: Katayama S, et al. Accuracy and Clinical Utility of a Tumor Grade- and Stage-based Predictive Model in Localized Upper Tract Urothelial Carcinoma. Eur Urol Focus (2021), https://doi.org/10.1016/j.euf.2021.05.002

Table 3 – Univariable and multivariable logistic regression with risk factors from the EAU and NCCN guidelines for prediction of localized upper tract urothelial carcinoma (≤pT1 and no lymph node metastasis)

	Univariable analysis		Multivariable analysis			
	OR (95% CI)	*p* value	EAU model		NCCN model	
			OR (95% CI)	*p* value	OR (95% CI)	*p* value
Hydronephrosis	0.68 (0.36–1.27)	0.22	0.58 (0.30–1.13)	0.11		
Tumor size (2.0 cm)	0.89 (0.48–1.64)	0.71	0.86 (0.46–1.60)	0.63		
Tumor size (1.5 cm)	0.55 (0.27–1.12)	0.10			0.47 (0.21–1.05)	0.07
Urinary cytology	0.57 (0.29–1.15)	0.12	0.50 (0.24–1.05)	0.50	0.60 (0.28–1.29)	0.19
Multifocality	1.28 (0.56–2.93)	0.56	1.14 (0.49–2.68)	0.76	1.29 (0.50–3.30)	0.60
Variant histology	0.63 (0.10–3.86)	0.62	0.55 (0.87–3.63)	0.55		
Previous RC	0.21 (0.18–2.32)	0.20	0.21 (2.05–6.91)	0.21		
Tumor architecture	0.44 (0.17–1.13)	0.09			0.43 (0.16–1.16)	0.10

EAU = European Association of Urology; NCCN = National Comprehensive Cancer Network; OR = odds ratio; CI = confidence interval; RC = radical cystectomy.

Table 4 – Diagnostic performance of each model for prediction of localized upper tract urothelial carcinoma (≤pT1 and no lymph node metastasis) among 560 patients

	GS model	EAU model	NCCN model
Suitable patients identified, *n* (%)	198 (35)	33 (6)	24 (4)
Sensitivity, % (95% CI)	49.5 (43.5–55.5)	8.2 (5.3–12.0)	7.1 (4.4–10.8)
Specificity, % (95% CI)	78.9 (73.6–83.5)	96.4 (93.5–98.3)	98.6 (96.4–99.6)
Positive predictive value, % (95% CI)	70.2 (63.3–76.5)	69.7 (51.3–84.4)	83.3 (62.6–95.3)
Negative predictive value, % (95% CI)	60.8 (55.5–65.8)	51 (46.7–55.4)	51.3 (47.0–55.6)
Accuracy, % (95% CI)	64.1 (60.0–68.1)	52.1 (47.9–56.3)	52.7 (48.4–56.9)
AUC (%)	71.2	74.6	75.2

GS = tumor grade- and stage-based model; EAU = European Association of Urology; NCCN = National Comprehensive Cancer Network; CI = confidence interval; AUC = area under the receiver operating characteristic curve.

pathologic examination of surgical specimens. The grade concordance rate between URS and RNU was 69.6%. In the overall cohort, we identified 198 patients (35%) who had low-grade tumors according to URS and no muscle invasion according to radiologic assessment. Of these, 139 patients (70%) had ≤pT1 and 59 (30%) had ≥pT2 disease.

As shown in Table 3, multivariable analyses revealed that none of the prognostic factors included in either the EAU or NCCN guidelines was associated with the presence of localized UTUC tumors in the group of patients with low-grade and low-stage UTUC. The predictive performance of each model is shown in Table 4. The GS, EAU, and NCCN models identified 198 (35%), 33 (6%), and 24 (4%) patients, with accuracy of 64.1%, 52.1%, and 52.7%, and AUC of 71.2%, 74.6%, and 75.2%, respectively; a comparison of the models is shown in Supplementary Figure 1. DCA revealed that for the probability threshold range of 0–20%, the net benefit of the three models was similar. By contrast, while the NCCN model was slightly superior for the probability threshold range of 20–40%, the GS and EAU models showed similar performance (Fig. 1). The results of the CART analysis are shown in Figure 2. The most decisive variable was urinary cytology findings. After splitting, terminal node 8 yielded the highest estimated probability (86%), resulting in 35 eligible patients (6%). We confirmed that the CART model with these four variables was not significantly associated with the presence of localized disease via multivariable analysis (Supplementary Table 1).

4. Discussion

We found that the risk factors defined in the EAU and NCCN guidelines were not associated with the presence of localized UTUC tumors among patients with low-grade, low-stage UTUC. In other words, they did not improve the predictive value beyond clinical stage and grade by a statistically significant margin. The GS model, based on URS biopsy and imaging findings, provided a predictive accuracy comparable to that of the EAU and NCCN models while yielding a reasonable number of patients who could be considered for KSS. In addition, we developed a sequential weighted selection tree using a CART model for decision-making and patient counseling.

In order to encourage clinicians to perform KSS without jeopardizing oncologic safety, guidelines have adopted restrictive risk management scenarios. There are inherent difficulties in accurately predicting tumor stage in patients with UTUC, with a significant risk of understaging or missing pathologically advanced tumors. Such risk management strategies carefully integrate identified risk factors for patient management [14–16]. Of these risk factors, tumor stage determined via imaging examinations has been found to be the most crucial independent factor [7,17]. Studies have shown that tumor grading via URS biopsy is also crucial because tumor grades are highly correlated with tumor stage in patients with UTUC [10,18]. However, owing to the nature of such a rare entity, other risk factors have

Please cite this article in press as: Katayama S, et al. Accuracy and Clinical Utility of a Tumor Grade- and Stage-based Predictive Model in Localized Upper Tract Urothelial Carcinoma. Eur Urol Focus (2021), https://doi.org/10.1016/j.euf.2021.05.002

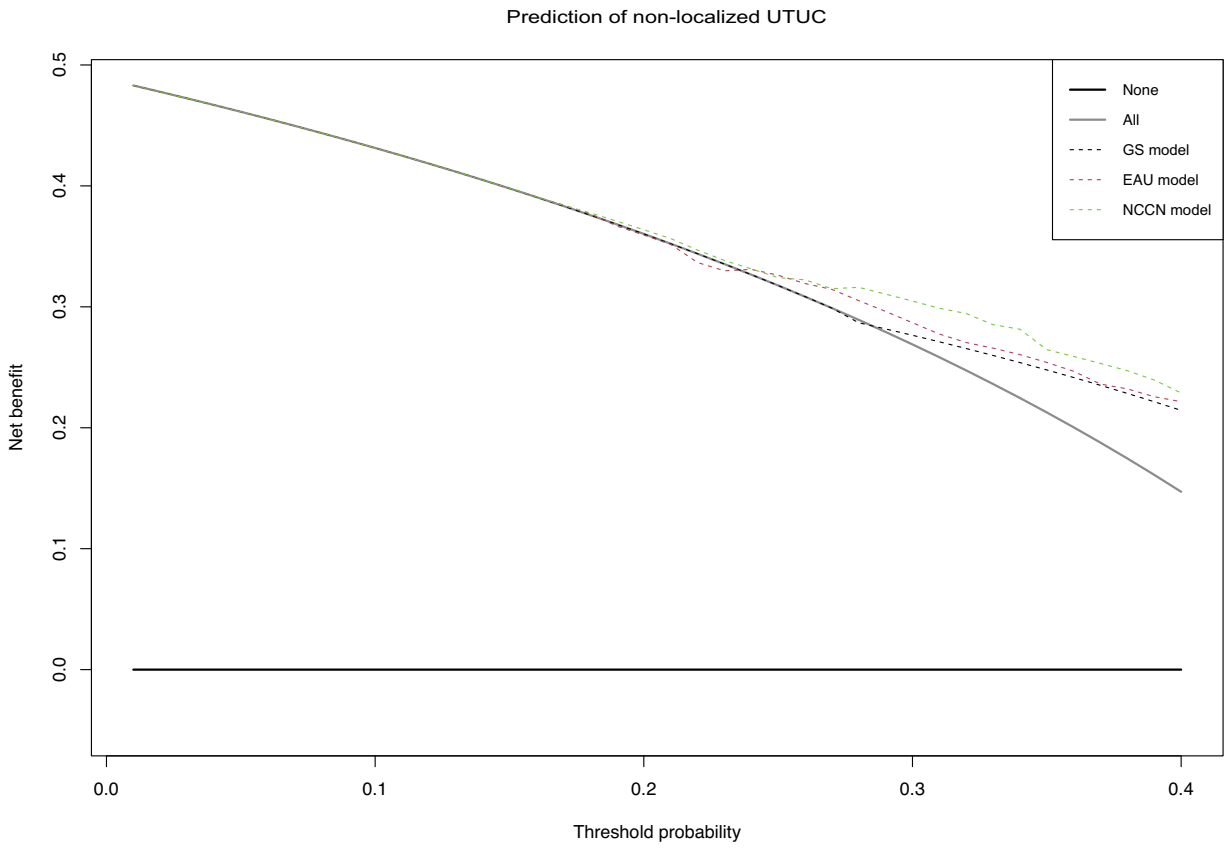


Fig. 1 – Decision curve analysis illustrating the net benefit of prediction of nonlocalized upper tract urothelial carcinoma (muscle-invasive or lymph node involvement) with the tumor grade- and stage-centered (GS) model and the European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) guideline models.

been identified, largely based on expert opinions and small, retrospective, single-institution studies, resulting in low levels of evidence [19]. For instance, urinary cytology findings have poor ability to predict muscle-invasive UTUC (sensitivity 62% and PPV of 44%) [15]. The value of hydronephrosis in predicting survival outcome also remains debatable [7]. We found that none of the risk factors recommended by the EAU and NCCN guidelines, except for tumor grade and stage, significantly added value to risk prediction in multivariable analyses for patients with clinically low-grade, non–muscle-invasive UTUC. Furthermore, although risk classification according to the EAU and NCCN guidelines resulted in high specificity (96.4% and 98.6%, respectively), the sensitivity was extremely low (8.2% and 7.1%, respectively). Therefore, despite the fact that 281 patients (50%) in the entire cohort had localized disease, fewer patients potentially eligible for KSS were identified by the EAU and NCCN models (6% and 4% of the entire cohort, respectively). Owing to the lower sensitivity, some patients may have unnecessarily undergone RNU (ie, overtreatment) with significant health-related consequences [20]. Furthermore, both the EAU and NCCN models had high AUC values despite their low accuracy, suggesting that they achieved high PPV for non–muscle-invasive UTUC at the cost of a high false-negative rate. Meanwhile, the GS model that only included URS-based tumor grade and imaging-based stage showed the highest accuracy (64.1%) and it had better sensitivity (49.5%) and provided a higher number of patients potentially eligible for KSS (35% of all patients) in comparison to the EAU and NCCN predictive models.

To date, several preoperative and postoperative models that focus on survival outcomes for muscle-invasive, non–organ-confined UTUC have been developed [7,10]. However, to the best of our knowledge, only the EAU and NCCN guideline models aim to specifically identify patients with low-risk disease supposed to harbor non–muscle-invasive UTUC. In our study, DCA showed that in the clinically plausible range of probability thresholds, the net benefits of the three predictive models were only marginally different, strongly suggesting that the GS model relying on only clinical stage and grade would be of use in clinical practice.

We also used a CART method to develop a sequential weighted selection tree that could assist in clinical decision-making and patient counseling. We found that as the number of factors included increased, the possibility of detecting localized UTUC increased and the number of patients potentially eligible for KSS decreased. Interestingly, in contrast to a previous study [21], in our selection tree, tumors >2 cm in size showed a higher possibility of being localized UTUC than those ≤2 cm. This finding suggests that in patients with tumors presumed to be of low risk on the basis of clinical stage and grade, tumors may grow only in the lumen without invasion of the muscular layers, implying that

Please cite this article in press as: Katayama S, et al. Accuracy and Clinical Utility of a Tumor Grade- and Stage-based Predictive Model in Localized Upper Tract Urothelial Carcinoma. Eur Urol Focus (2021), https://doi.org/10.1016/j.euf.2021.05.002

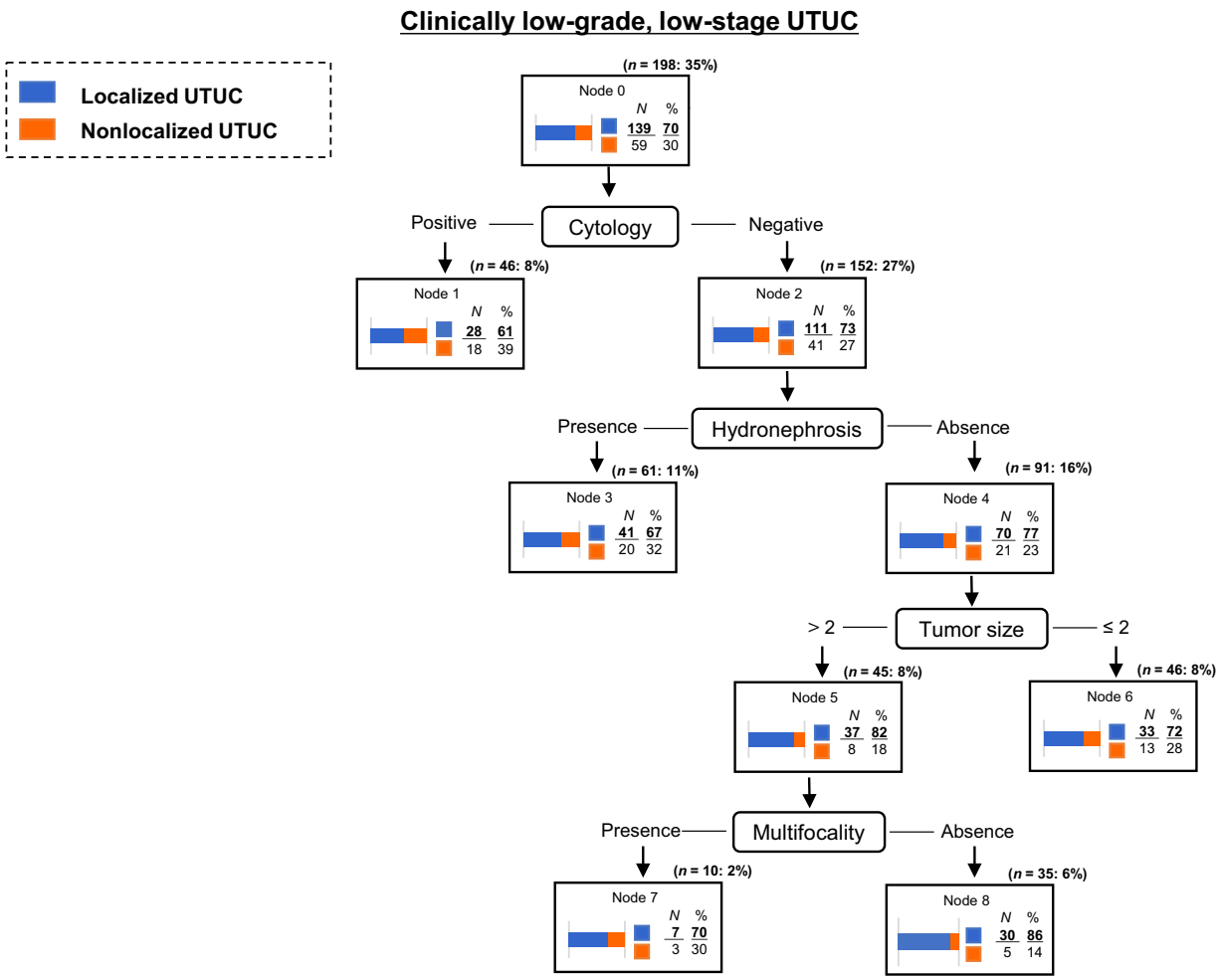


Fig. 2 – Classification and regression tree (CART)–based weighted selection tree for prediction of non–muscle-invasive upper tract urothelial carcinoma (UTUC).

tumor size might not be correlated with the presence of advanced UTUC [22]. It is of utmost importance to balance the potential benefits of preserving the kidney with the risk of undertreatment, and to balance diagnostic accuracy with the number of patients eligible for KSS. Therefore, the optimal personalized treatment strategy (KSS vs RNU) should be chosen via shared decision-making after patient counseling, taking into consideration factors such as each patient's life expectancy, comorbidities, and preferences.

So far, all guidelines have proposed risk assessment based on widely used clinicopathologic features. Biomarkers that capture the biological and clinical potential of each tumor would help to improve treatment by a large degree [23]. Molecular characterization studies revealed a high-frequency *FGFR* mutation in low-grade UTUC tumors (92%), providing insights that could lead to a potential improvement in survival outcomes [24,25]. Similarly, mRNA expression subtypes may help to refine tumor classification to drive therapy [26,27]. Further investigation to clarify the molecular profile may improve our understanding of UTUC biology and help in the development of rational and precise risk-stratification strategies as well as effective targets.

Every attempt to enhance diagnostic accuracy results in a decrease in the number of eligible patients. While our GS model is not perfect, it is quite simple to apply. Considering the priorities of individual patients, such as preference for avoiding either RNU and consequent dialysis or disease progression, combined with the probability of localized UTUC obtained via the CART model, we could determine a successful individualized treatment for each case. Furthermore, clinicians could find their own acceptable probabilities using the CART model.

We acknowledge that the study has some limitations. First, the retrospective nature could have introduced selection bias. Patients who received KSS treatment were not included in the study, so the number of patients eligible for KSS was potentially underestimated. However, the large majority of nonimpactive cases underwent RNU during the study period, decreasing the magnitude of the selection bias and making a Will Rogers phenomenon unlikely. Moreover, the number of patients for whom risk assessment was performed using the EAU and NCCN models was small. This is supported by the substantial number of patients who were confirmed to have pathologically localized UTUC

Please cite this article in press as: Katayama S, et al. Accuracy and Clinical Utility of a Tumor Grade- and Stage-based Predictive Model in Localized Upper Tract Urothelial Carcinoma. Eur Urol Focus (2021), https://doi.org/10.1016/j.euf.2021.05.002

(50%). Second, our findings showed a higher rate of tumor upgrading (54%) than in previous studies (31–51%), but this is an inherent limitation and finding that varies across studies [28,29]. Third, we could not consider the probability of recurrence for KSS. Nevertheless, the GS model showed satisfactory predictive accuracy, probably because imaging-based tumor staging complements this inherent limitation. Considering this and the multi-institutional nature of the study, our concept could be worthy of generalization and further investigation.

5. Conclusions

In conclusion, our multi-institutional international cohort study of risk factors in UTUC tumors revealed that the risk factors proposed by the EAU and NCCN guidelines do not provide sufficient additive value in predicting a favorable pathologic outcome for patients with clinically low-grade, non–muscle-invasive UTUC. The balance between avoiding unnecessary kidney loss (ie, overtreatment) and under-treatment is delicate in clinical practice and requires consideration of biomarkers and patient factors, as well as patient preferences. We believe that our stage- and grade-centered model provides a framework to improve the personalization of UTUC treatment and achieves a more realistic balance between KSS and RNU. Our model could serve as an easy and reproducible guide for discussions underlying shared decision-making with patients regarding the optimal management strategy for their tumors.

Author contributions: Satoshi Katayama 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: Katayama, Araki, Shariat.
Acquisition of data: Moschini, Grossmann, Margulis, Enikeev, Compérat.
Analysis and interpretation of data: Schuettfort, Motlagh, Karakiewicz.
Drafting of the manuscript: Katayama, Mori, Quhal.
Critical revision of the manuscript for important intellectual content: Pradere, Abufaraj, Teoh, Rouprêt.
Statistical analysis: Laukhtina.
Obtaining funding: None.
Administrative, technical, or material support: Mostafaei, Rajwa.
Supervision: Nasu, Shariat.
Other: None.

Financial disclosures: Satoshi Katayama certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

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.euf.2021.05.002.

References

[1] Favaretto RL, Shariat SF, Chade DC, et al. The effect of tumor location on prognosis in patients treated with radical nephroureterectomy at Memorial Sloan-Kettering Cancer Center. Eur Urol 2010;58:574–80.
[2] Roscigno M, Shariat SF, Margulis V, et al. The extent of lymphadenectomy seems to be associated with better survival in patients with nonmetastatic upper-tract urothelial carcinoma: how many lymph nodes should be removed? Eur Urol 2009;56:512–8.
[3] Rouprêt M, Babjuk M, Burger M, et al. European Association of Urology guidelines on upper urinary tract urothelial carcinoma: 2020 update. Eur Urol 2021;79:62–79.
[4] Xylinas E, Rink M, Cha EK, et al. Impact of distal ureter management on oncologic outcomes following radical nephroureterectomy for upper tract urothelial carcinoma. Eur Urol 2014;65:210–7.
[5] Schuettfort VM, Pradere B, Quhal F, et al. Diagnostic challenges and treatment strategies in the management of upper-tract urothelial carcinoma. Turk J Urol 2021;47(Suppl 1):S33–44.
[6] National Comprehensive Cancer Network. Bladder cancer version 6, 2020. https://www.nccn.org/professionals/physician_gls/pdf/bladder_blocks.pdf.
[7] Favaretto RL, Shariat SF, Savage C, et al. Combining imaging and ureteroscopy variables in a preoperative multivariable model for prediction of muscle-invasive and non-organ confined disease in patients with upper tract urothelial carcinoma. BJU Int 2012;109:77–82.
[8] Margulis V, Youssef RF, Karakiewicz PI, et al. Preoperative multivariable prognostic model for prediction of nonorgan confined urothelial carcinoma of the upper urinary tract. J Urol 2010;184:453–8.
[9] Upfill-Brown A, Lenis AT, Faiena I, et al. Treatment utilization and overall survival in patients receiving radical nephroureterectomy versus endoscopic management for upper tract urothelial carcinoma: evaluation of updated treatment guidelines. World J Urol 2019;37:1157–64.
[10] Brien JC, Shariat SF, Herman MP, et al. Preoperative hydronephrosis, ureteroscopic biopsy grade and urinary cytology can improve prediction of advanced upper tract urothelial carcinoma. J Urol 2010;184:69–73.
[11] 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.
[12] Cutress ML, Stewart GD, Tudor EC, et al. Endoscopic versus laparoscopic management of noninvasive upper tract urothelial carcinoma: 20-year single center experience. J Urol 2013;189:2054–60.
[13] Lughezzani G, Jeldres C, Isbarn H, et al. A critical appraisal of the value of lymph node dissection at nephroureterectomy for upper tract urothelial carcinoma. Urology 2010;75:118–24.
[14] Raman JD, Ng CK, Scherr DS, et al. Impact of tumor location on prognosis for patients with upper tract urothelial carcinoma managed by radical nephroureterectomy. Eur Urol 2010;57:1072–9.
[15] Messer J, Shariat SF, Brien JC, et al. Urinary cytology has a poor performance for predicting invasive or high-grade upper-tract urothelial carcinoma. BJU Int 2011;108:701–5.
[16] Zigeuner R, Shariat SF, Margulis V, et al. Tumour necrosis is an indicator of aggressive biology in patients with urothelial carcinoma of the upper urinary tract. Eur Urol 2010;57:575–81.
[17] Shariat SF, Zigeuner R, Rink M, et al. Subclassification of pT3 urothelial carcinoma of the renal pelvicalyceal system is associated with recurrence-free and cancer-specific survival: proposal for a revision of the current TNM classification. Eur Urol 2012;62:224–31.
[18] 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.

Please cite this article in press as: Katayama S, et al. Accuracy and Clinical Utility of a Tumor Grade- and Stage-based Predictive Model in Localized Upper Tract Urothelial Carcinoma. Eur Urol Focus (2021), https://doi.org/10.1016/j.euf.2021.05.002

[19] Chromecki TF, Bensalah K, Remzi M, et al. Prognostic factors for upper urinary tract urothelial carcinoma. Nat Rev Urol 2011;8:440–7.
[20] Xylinas E, Rink M, Margulis V, et al. Impact of renal function on eligibility for chemotherapy and survival in patients who have undergone radical nephro-ureterectomy. BJU Int 2013;112:453–61.
[21] Shibing Y, Liangren L, Qiang W, et al. Impact of tumour size on prognosis of upper urinary tract urothelial carcinoma after radical nephroureterectomy: a multi-institutional analysis of 795 cases. BJU Int 2016;118:902–10.
[22] Foerster B, Abufaraj M, Mari A, et al. The performance of tumor size as risk stratification parameter in upper tract urothelial carcinoma (UTUC). Clin Genitourin Cancer. In press. DOI: 10.1016/j.clgc.2020.09.002.
[23] Rink M, Chun FK, Dahlem R, et al. Prognostic role and HER2 expression of circulating tumor cells in peripheral blood of patients prior to radical cystectomy: a prospective study. Eur Urol 2012;61:810–7.
[24] Moss TJ, Qi Y, Xi L, et al. Comprehensive genomic characterization of upper tract urothelial carcinoma. Eur Urol 2017;72:641–9.
[25] van Oers JM, Zwarthoff EC, Rehman I, et al. FGFR3 mutations indicate better survival in invasive upper urinary tract and bladder tumours. Eur Urol 2009;55:650–7.
[26] Hassler MR, Bray F, Catto JWF, et al. Molecular characterization of upper tract urothelial carcinoma in the era of next-generation sequencing: a systematic review of the current literature. Eur Urol 2020;78:209–20.
[27] Robinson BD, Vlachostergios PJ, Bhinder B, et al. Upper tract urothelial carcinoma has a luminal-papillary T-cell depleted contexture and activated FGFR3 signaling. Nat Commun 2019;10:2977.
[28] Wang L, Pambuccian SE, Wojcik EM, et al. Diagnosis of upper tract urothelial carcinoma-a comparative study of urinary cytology and surgical biopsy. J Am Soc Cytopathol 2015;4:3–9.
[29] Margolin EJ, Matulay JT, Li G, Meng X, et al. Discordance between ureteroscopic biopsy and final pathology for upper tract urothelial carcinoma. J Urol 2018;199:1440–5.

Please cite this article in press as: Katayama S, et al. Accuracy and Clinical Utility of a Tumor Grade- and Stage-based Predictive Model in Localized Upper Tract Urothelial Carcinoma. Eur Urol Focus (2021), https://doi.org/10.1016/j.euf.2021.05.002