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Risk-adapted scoring model to identify candidates benefiting from adjuvant chemotherapy after radical nephroureterectomy for localized upper urinary tract urothelial carcinoma: A multicenter study

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Purpose: Adjuvant chemotherapy (AC) is recommended for muscle-invasive or lymph node-positive upper urinary tract urothelial carcinoma (UTUC) after radical nephroureterectomy (RNU). However, disease recurrences are frequently observed in pT1 disease, and AC may increase the risk of overtreatment in pT2 UTUC patients. This study aimed to validate a risk-adapted scoring model for selecting UTUC patients with ≤pT2 disease who would benefit from AC.

Materials and Methods: We retrospectively analyzed 443 ≤pT2 UTUC patients who underwent RNU. A risk-adapted scoring model was applied, categorizing patients into low- or high-risk groups. Recurrence-free survival (RFS) and cancer-specific survival (CSS) were analyzed according to risk group.

Results: Overall, 355 patients (80.1%) and 88 patients (19.9%) were categorized into the low- and high-risk groups, respectively, with the latter having higher pathological stages, concurrent carcinoma *in situ,* and synchronous bladder tumors. Disease recurrence occurred in 45 patients (10.2%), among whom 19 (5.4%) and 26 (29.5%) belonged to the low- and high-risk groups, respectively (p<0.001). High-risk patients had significantly shorter RFS (64.3% vs. 93.6% at 60 months; hazard ratio [HR] 13.66; p<0.001) and worse CSS (80.7% vs. 91.5% at 60 months; HR 4.25; p=0.002). Multivariate analysis confirmed that pT2 stage and the high-risk group were independent predictors of recurrence and cancer-specific death (p<0.001). Decision curve analysis for RFS showed larger net benefits with our model than with the T stage model.

Conclusions: The risk-adapted scoring model effectively predicts recurrence and identifies optimal candidates for AC post RNU in non-metastatic UTUC.

Keywords: Chemotherapy, adjuvant; Nephroureterectomy; Renal pelvis; Risk factor scores; Ureteral neoplasms

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INTRODUCTION

Upper urinary tract urothelial carcinoma (UTUC) is uncommon, accounting for only 5% of all urothelial tumors [1]. Radical nephroureterectomy (RNU) with bladder cuff excision has been regarded as the standard treatment for patients with non-metastatic UTUC [2,3]. However, approximately 25% of patients with UTUC experience disease recurrence or metastasis after surgical treatment, leading to poor survival outcomes [4]. Although a number of retrospective studies have investigated the potential of cisplatin-based adjuvant chemotherapy (AC) after RNU to overcome such poor outcomes, high-level evidence of its effectiveness during last decade has been lacking. Recently, the results of the POUT trial, a phase 3 randomized controlled trial, found that AC after RNU significantly improved disease-free survival in patients with locally advanced UTUC [5].

Based on the results of the POUT trial, AC has been recommended for either muscle-invasive (pT2–pT4, pN_{any}) or lymph node-positive (pT_{any}, pN1–N3) UTUC after RNU [2,3]. However, the POUT trial found that the survival benefits of AC in pT2 was not greater than that in pT3 or lymph node-positive disease. In this regard, administering systemic therapy to all pT2 UTUC patients with low potential for recurrence could place them at risk of overtreatment. In addition, disease recurrence and metastasis are quite common in clinical practice even among patients diagnosed with localized pT1 disease [4,6]. However, simple periodic surveillance for recurrence without adjuvant treatment among patients with pT1 at high-risk for recurrence would likely result in undertreatment. Therefore, identifying the optimal target patients for AC after RNU is paramount.

Although several prognostic nomograms have been proposed for AC in high-risk UTUC, their actual clinical use has major limitations due to the complexity and diversity of the nomograms [7-9]. To provide more effective evidence-based treatment, we developed and proposed a simple risk-adapted scoring model for adjuvant systemic therapy in localized UTUC with ≤pT2 disease by adopting and modifying the risk-adapted scoring model for non-metastatic UTUC in the EAU guideline (Table 1). This multicenter study therefore aimed to validate the developed risk-adapted scoring model for the selection of non-metastatic UTUC patients with ≤pT2 disease who would benefit from AC.

MATERIALS AND METHODS

1. Risk-adapted scoring model for adjuvant systemic therapy after RNU in non-metastatic UTUC

The risk-adapted scoring model to identify non-metastatic UTUC patients with ≤pT2 disease who would benefit from AC is displayed in Table 1. This model consists of seven risk factors, namely (1) high-grade tumor, (2) tumor size ≥2 (cm), (3) multifocal disease, (4) local invasion on computed tomography urography (CTU), (5) hydronephrosis, (6) previous history for bladder urothelial carcinoma, and (7) variant histology. Among the seven risk factors, six clinicopathologic factors had been proposed as risk factors in the risk-adapted scoring model for non-metastatic UTUC in the European Association of Urology (EAU) guideline [2], except for one risk factor, which was modified from "history of previous radical cystectomy for high-risk bladder cancer" to "previous history for bladder urothelial carcinoma." Each risk factor was assigned 1 point, and the sum of risk factors for each patient was scored and divided into a low-risk group (1–3 points) and high-risk group (≥4 points) for disease recurrence. Patients in the high-risk group were considered candidates for AC after RNU.

2. Patients

We retrospectively identified 792 patients who underwent RNU for UTUC between February 2007 and December 2020 at three tertiary care centers in South Korea. The inclusion criteria were as follows: (1) pathologic diagnosis of urothelial carcinoma in the renal pelvic or ureter, (2) pathologic tumor stage a-2 with no clinical evidence of lymph node or distant metastasis, and (3) no evidence of disease recurrence within 3 months after surgery. The exclusion cri-

Table 1. Risk-adapted scoring model for adjuvant systemic therapy in localized UTUC (≤pT2)

Risk factor (1 point for each factor)
High-grade tumor
Tumor size ≥2 cm
Multifocal disease
Local invasion on CTU
Hydronephrosis
Previous history for bladder urothelial carcinoma
Variant histology

Risk group: A score of 1–3 points indicates low risk of disease recurrence, while a score of 4 or more points indicates high risk.
UTUC, urinary tract urothelial carcinoma; CTU, computed tomography urography.

teria were as follows: (1) patients with previous or sequential second primary cancers (except for bladder tumor), (2) those who did not undergo RNU, and (3) those who received systemic therapy during the perioperative period. Ultimately, 443 patients with pTa-2N0M0 UTUC following RNU were analyzed. All patients underwent RNU with bladder cuff resection via the open, laparoscopic, or robotic approach according to the surgeon's preference. Bladder cuff resection was performed through the extravesical approach [10]. Lymphadenectomy was not routinely performed, except in patients with suspiciously enlarged lymph nodes on preoperative imaging. Ethical board review approval was obtained from each institution before clinical data collection. The study protocol was conducted in accordance with the ethical guidelines of the Declaration Helsinki (2013) and approved by the Institutional Review Board (IRB) of Inje University Busan Paik Hospital (approval number: BPIRB 2023-04-007). The requirement for informed consent was waived by the IRB due to the retrospective nature of the study.

Patients were followed-up every 3 months for the first year after RNU, every 6 months after the first year up to 5 years after RNU, and then annually thereafter. The follow-up evaluations included cystoscopy, serum laboratory tests, urine tests (including urine cytology), and abdominal and chest computed tomography or magnetic resonance imaging. Disease recurrence was defined as new lesions >10 mm in size that were previously undetected by radiologic evaluation. Disease recurrence included locoregional recurrence at the ipsilateral surgical field or distant metastasis defined as disease recurrence outside of the locoregional surgical field or in other organs. Intravesical recurrence was not considered to indicate disease recurrence.

3. Data collection

Collected data included age, sex, tumor size and multifocality, CTU invasion, preoperative hydronephrosis, pathologic tumor staging and grading, presence of variant histology, and disease recurrence status. Preoperative hydronephrosis was determined based on preoperative radiologic findings from CTU or magnetic resonance imaging. CTU invasion was defined as infiltration into the renal parenchyma, renal sinus fat, or periureteric tissue on cross sectional imaging [11].

4. Pathologic evaluation

All specimens were histologically confirmed by a genitourinary pathologist with over 10 years of experience in each institution. Tumors were staged according to the seventh and eighth American Joint Committee on Cancer tumor-node-metastasis classification and graded according to the 2004 and 2016 World Health Organization (WHO) classifications [12-15]. Variant histology was considered under a previously reported reference that is well accepted by the uropathological community and WHO classifications [12,14,16]. Tumor size was measured based on the largest dimension determined using macroscopic and microscopic examinations of single tumor frozen sections. If tumor multifocality was present, the largest tumor diameter was taken for analysis. The tumor location was defined as the renal pelvis, ureter, or both the renal pelvis and ureter. Tumor multifocality was defined as pathologic confirmation of the synchronous presence of tumors in any location within the upper urinary tract. Lymphovascular invasion and concomitant carcinoma *in situ* status was also evaluated.

5. Statistical analysis

Continuous variables were presented as means with standard deviations or medians with interquartile range (IQR), whereas categorical variables are presented as frequencies with percentages. Differences in the distribution of variables among groups were evaluated using the chi-square test, Fisher's exact test and linear-by-linear association for categorical variables and Student's t-test and one-way ANOVA for continuous variables. Probabilities of recurrence-free survival (RFS) and cancer-specific survival (CSS) were estimated using the Kaplan–Meier method and compared using the log-rank test. Univariate and multivariate Cox proportional hazards regression models were utilized to identify any clinicopathological factors that might have affected disease recurrence and survival. Risk was expressed as hazard ratios (HRs), and 95% confidence intervals (CIs) were determined using the reference groups. Finally, decision curve analysis (DCA) was applied to evaluate the clinical validity of the risk-adapted scoring model [17,18]. Statistical analysis was conducted using IBM SPSS Statistics version 27.0 (IBM Corp.), Medcalc version 22.0 (MedCalc Software Ltd.), or the "dcurves" package in R statistical package version 4.2.3 (R Foundation for Statistical Computing, https://www.r-project.org). All tests were two-sided, with a $p<0.05$ indicating statistical significance.

RESULTS

Overall, 443 non-metastatic UTUC patients with ≤pT2 disease who underwent RNU were include for analysis. The median follow-up duration for the cohort was 39.2 months (IQR 3.6–134.5 months), and 31 patients (7.0%) had died throughout the study period. Table 2 summarizes the clinicopathologic characteristics of the include patients stratified

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Table 2. Comparison of baseline clinicopathologic characteristics (n=443)

Characteristic	Risk group		p-value
	Low-risk	High-risk	
Number of patients	355 (80.1)	88 (19.9)	
Age (y)	71 (42–88)	72 (47–88)	0.893
Sex			0.083
Male	256 (72.1)	55 (62.5)	
Female	99 (27.9)	33 (37.5)	
Body mass index (kg/m^2)	24.2 (17.3–31.9)	24.0 (16.9–31.2)	0.833
Diabetes mellitus			0.241
Absent	264 (74.4)	60 (68.2)	
Present	91 (25.6)	28 (31.8)	
Hypertension			0.982
Absent	182 (51.3)	45 (51.1)	
Present	173 (48.7)	43 (48.9)	
ECOG performance status			0.450
0–1	331 (93.2)	80 (90.9)	
≥2	24 (6.8)	8 (9.1)	
History of bladder urothelial carcinoma			<0.001
Absent	341 (96.1)	68 (77.3)	
Present	14 (3.9)	20 (22.7)	
Hydronephrosis			<0.001
Absent	188 (53.0)	7 (8.0)	
Present	167 (47.0)	81 (92.0)	
CTU invasion			<0.001
Absent	332 (93.5)	39 (44.3)	
Present	23 (6.5)	49 (55.7)	
Operation method			0.920
Open	58 (16.3)	15 (17.0)	
Laparoscopic	264 (74.4)	66 (75.0)	
Robotic	33 (9.3)	7 (8.0)	
LN dissection during NUx.			0.353
No	336 (94.6)	81 (92.0)	
Yes	19 (5.4)	7 (8.0)	
Tumor location			<0.001
Pelvicalyceal	187 (52.7)	30 (34.1)	
Ureter	163 (45.9)	43 (48.9)	
Both	5 (1.4)	15 (17.0)	
Tumor size (cm)	2.7 (0.5–7.0)	3.5 (0.5–7.3)	<0.001
Pathologic tumor stage			<0.001
Ta/is	125 (35.2)	8 (9.1)	
T1	161 (45.4)	41 (46.6)	
T2	69 (19.4)	39 (44.3)	
Pathologic grading			<0.001
Low-grade	131 (36.9)	4 (4.5)	
High-grade	224 (63.1)	84 (95.5)	
Variant histology			<0.001
Absent	345 (97.2)	75 (85.2)	
Present	10 (2.8)	13 (14.8)	

Table 2. Continued

Characteristic	Risk group		p-value
	Low-risk	High-risk	
Lymphovascular invasion			0.090
Absent	342 (96.3)	81 (92.0)	
Present	13 (3.7)	7 (8.0)	
Multifocality			<0.001
Absent	334 (94.1)	38 (43.2)	
Present	21 (5.9)	50 (56.8)	
Concomitant CIS			0.001
Absent	310 (87.3)	64 (72.7)	
Present	45 (12.7)	24 (27.3)	
Synchronous bladder tumor			0.006
Absent	308 (86.8)	66 (75.0)	
Present	47 (13.2)	22 (25.0)	
Positive ureteral resection margin			0.166
Absent	346 (97.5)	83 (94.3)	
Present	9 (2.5)	5 (5.7)	

Values are presented as number (%) or median (interquartile range).
ECOG, Eastern Cooperative Oncology Group; CTU, computed tomography urography; LN, lymph node; NUx., nephroureterectomy; CIS, carcinoma *in situ*.

according to risk group. Among the 443 patients, 88 (19.9%) were categorized into the high-risk group. Notably, 39 (36.1%) of the 108 pT2 patients and 49 (14.6%) of the 335 ≤pT1 patients were categorized into the high-risk group. No significant difference in age at surgery, body mass index, baseline comorbidities, surgical methods, and resection margin status were observed among the included patients (all, p>0.05). The high-risk group presented with a higher pathological tumor stage (p<0.001), more concomitant carcinoma *in situ* (p=0.001), and more synchronous bladder tumors during RNU (p=0.006) than did the low-risk group.

Overall, 45 patients (10.2%) experienced disease recurrence. In particular, 27 (25.0%) of the 108 pT2 patients and 18 (5.4%) of the 335 ≤pT1 patients experienced disease recurrence. Moreover, 19 patients (5.4%) and 26 patients (29.5%) in the low- and high-risk groups experienced disease recurrence, respectively (p<0.001). Neither group reached the median RFS and CSS (Fig. 1). The risk for disease recurrence was significantly higher in the high-risk group than in the low-risk group (HR 13.66, 95% CI 6.43–29.03, p<0.001). The estimated percentage of patients who remained recurrence-free at 60 months was 64.3% (95% CI 63.6–64.9) in the high-risk group and 93.6% (95% CI 93.4–93.8) in the low-risk group. Similarly, the high-risk group showed worse CSS than did the low-risk group (HR 4.25, 95% CI 1.68–10.71, p=0.002), with the probability of CSS at 60 months being 80.7% (95% CI 80.1–81.3) in the high-risk group and 91.5% (95% CI 91.3–91.7) in the low-risk group.

Multivariate Cox regression analysis showed that pT2 stage (HR 3.98, 95% CI 2.14–7.42, p<0.001) and the high-risk group (HR 4.29, 95% CI 2.32–7.95, p<0.001) were predictors of disease recurrence. Regarding CSS, pT2 stage (HR 2.13, 95% CI 1.00–4.56, p=0.049) and the high-risk group (HR 2.56, 95% CI 1.22–5.38, p=0.012) were identified as predictors of poor CSS (Table 3).

DCA for 5- and 7-year RFS probability were applied to verify the clinical utility of the risk-adapted scoring model for predicting disease recurrence. Notably, DCA showed that the risk-adapted scoring model showed larger net benefits across a wider range of threshold probabilities than did the T stage model in our cohort, indicating that the risk-adapted scoring model had better clinical effectiveness in selecting candidates for AC (Fig. 2).

DISCUSSION

The current study aimed to establish and validate a simple risk-adapted scoring model for selecting non-metastatic UTUC patients with ≤pT2 disease who would benefit from AC after RNU. Interestingly, our study demonstrated that high-risk patients identified based on the risk-adapted scoring model were candidates for AC after RNU and that the proposed risk-adapted scoring model could help clinicians make appropriate decisions in pursuit of tailored individual

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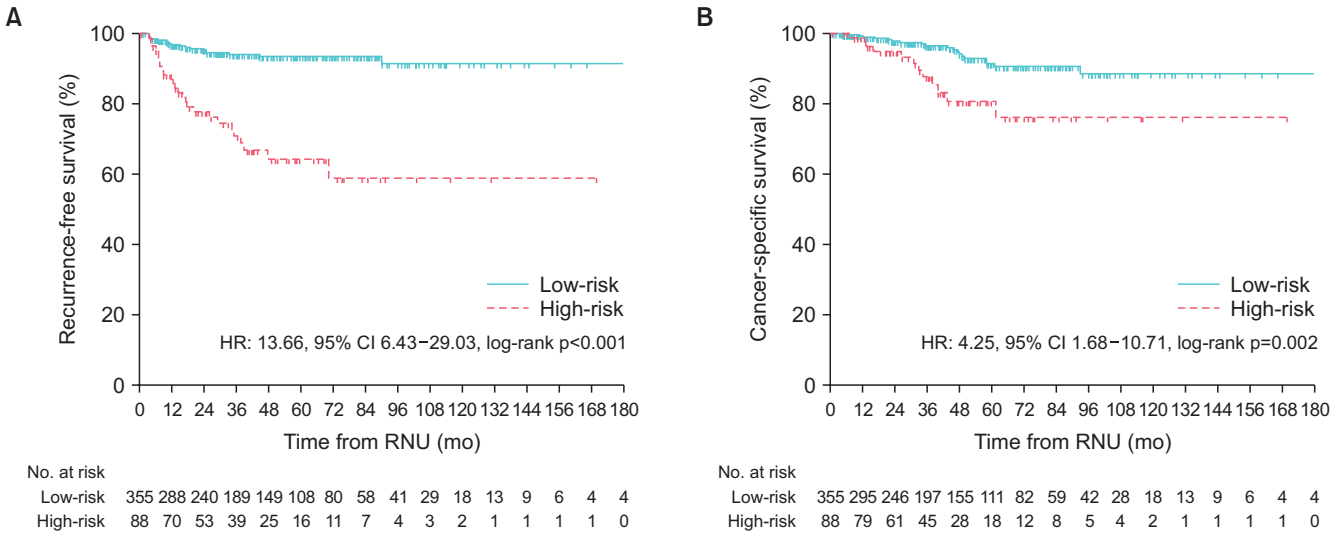

Fig. 1. Kaplan–Meier survival curves for recurrence-free survival (A) and cancer-specific survival (B) stratified according to risk groups (low-risk: 1–3 points, high-risk: ≥4 points). HR, hazard ratio; CI, confidence interval; RNU, radical nephroureterectomy.

patient care.

To date, several studies have investigated the efficacy of adjuvant treatment following surgical treatment of UTUC [19]. Given the low prevalence of UTUC, most previous studies were retrospective in nature and had small sample sizes. A recent randomized controlled trial, namely the POUT trial, investigated the effects of AC within 90 days of surgery for UTUC. This particular trial included 261 patients with either muscle-invasive (pT2–pT4, pN_{any}) or lymph node-positive (pT_{any}, pN1–N3) and provided an AC regimen containing cisplatin or carboplatin and gemcitabine [5]. During the median follow-up of 30.3 months, patients treated with AC after RNU showed better disease-free survival and metastasis-free survival than did those who only received surveillance. Notably, a follow-up analysis of the POUT trial showed that improvements in survival had been continuously maintained throughout the median follow-up of 48.1 months [20]. These results have driven changes in the treatment plan for UTUC. Specifically, platinum-based AC has been recommended in ≥pT2 or node-positive UTUC after RNU [2,3]. However, the subgroup analysis of the POUT trial should be considered more thoroughly. Although no heterogeneity in treatment effect with regard to disease-free survival had been observed according to prespecified balancing of tumor stage, AC did not show significant survival benefits in UTUC patient with pT2 disease. Furthermore, in actual clinical practice, UTUC patients with pT1 disease frequently experience recurrence or metastasis after RNU. As such, a risk-adapted scoring model is needed to avoid unnecessary adjuvant treatment in pT2 patients with low-risk of recurrence and identify ≤pT1 patients at high-risk of recurrence who require AC.

To facilitate effective and evidence-based treatment, several risk stratification models that aim to identify non-metastatic UTUC patients who are more likely to benefit from kidney-sparing surgery have been assessed [21,22]. Prognostic nomograms based on preoperative factors and postoperative pathological characteristics have also been available [7-9] and may be used when counseling patients regarding follow-up and administration of perioperative chemotherapy. However, the actual clinical utility of these nomograms has been limited due to their complexity and diversity. Hence, we developed a simple risk-adapted scoring model for adjuvant systemic therapy in localized UTUC with ≤pT2 disease by adopting and modifying the risk stratification model for non-metastatic UTUC in the EAU guideline [2]. Our model includes seven clinicopathological parameters routinely available in the pathology or radiographic reports throughout the perioperative period. The difference between the risk stratification model in the EAU guideline and our model is that we modified and integrated some factors and organized a scoring system to set the cutoff value and divide patients into risk groups. Among the eight risk factors in the original model, "high-grade in ureteroscopic biopsy" and "high-grade cytology" were combined into "high-grade tumor" in our model, whereas "previous radical cystectomy for high-grade bladder cancer" was changed to "history of bladder cancer." All risk factors have been found to be significant prognostic factors for both disease recurrence and CSS (Supplementary Table 1) [23,24]. Our model has a major advantage given that it can be used easily in clinical practice through a simple summation of risk factors. We observed clear differences in

Table 3. Univariate and multivariate Cox proportional hazard regression analyses for recurrence-free and cancer specific survival (n=443)

Variable	Recurrence-free survival				Cancer-specific survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.01 (0.97–1.04)	0.552			1.04 (1.00–1.08)	0.040	1.04 (0.99–1.09)	0.053
Sex (female)	1.23 (0.66–2.31)	0.505			0.99 (0.45–2.16)	0.996		
Synchronous bladder tumor	1.68 (0.85–3.31)	0.135			1.88 (0.84–4.21)	0.123		
Concomitant CIS	1.44 (0.69–2.99)	0.327			1.29 (0.49–3.37)	0.598		
Lymphovascular invasion	1.66 (0.51–5.38)	0.392			2.37 (0.72–7.81)	0.154		
Positive ureteral resection margin	2.91 (1.04–8.14)	0.051			3.00 (0.91–9.91)	0.071		
T stage (pT2)	5.68 (3.13–10.34)	<0.001	3.98 (2.14–7.42)	<0.001	3.05 (1.50–6.19)	0.002	2.13 (1.00–4.56)	0.049
Risk adapted score (high-risk)	6.08 (3.36–11.02)	<0.001	4.29 (2.32–7.95)	<0.001	2.95 (1.43–6.11)	0.003	2.56 (1.22–5.38)	0.012

HR, hazard ratio; CI, confidence interval; CIS, carcinoma *in situ*.

RFS and CSS between the low- and high-risk groups by examining survival rates based on our model.

Numerous studies have established LVI as a crucial factor significantly influencing disease recurrence and CSS in UTUC [25]. However, in our study, LVI was not utilized as a key prognostic factor. This decision was based on our regression analysis, which revealed that LVI was not a significant predictor of RFS and CSS. We postulate that this outcome may be attributed to the composition of our patient cohort. In our study, LVI was present in only 4.5% of patients, a considerably lower proportion compared to the 20% typically reported in invasive UTUC [2]. It is important to note that our study population consisted exclusively of patients with pT2 or lower stage tumors. Considering that the likelihood of detecting LVI in pathological specimens increases with higher pT stages in UTUC [26], the exclusion of LVI as a factor in our results, which focused on non-metastatic UTUC, appears to be a logical consequence of our study design and patient selection criteria.

In the current study, 5.4% of ≤pT1 patients and 25% of pT2 patients developed disease recurrence. Had the candidates for AC been selected based on pathologic tumor stage according to the POUT trial findings, 75% of pT2 patients would have been at risk of overtreatment, and approximately 5% of ≤pT1 patients would have been at risk for receiving insufficient treatment. Of particular interest are the approximately 5% of ≤pT1 patients who experienced disease recurrence or progression. Some of these patients, classified as high-risk group based on our study results, did not receive AC due to their low-stage tumors (T1 or Ta). As a result, they missed opportunities to prevent disease recurrence or progression. The significance of our study lies in its potential to identify patients who might be overlooked if selection is based solely on pathologic tumor stage. By applying our results, clinicians can more effectively recognize and treat high-risk patients, potentially improving outcomes in UTUC management.

To justify the clinical usefulness of the risk-adapted scoring model, we assessed weather decisions assisted by our model would improve patient outcomes. Notably, almost all the decision curves of our model for the 5- and 7-year RFS probabilities were above those for the tumor stage model. Moreover, a significant increase in the prevalence of pT2 disease was noted in patients with multiple risk factors, and multivariate analysis showed that the high-risk group was a better predictor for RFS and CSS than the pT2 tumor stage. These findings indicate that our risk-adapted scoring model could aid in making decisions tailored to individual patient care by identifying patients with pT2 disease who may have

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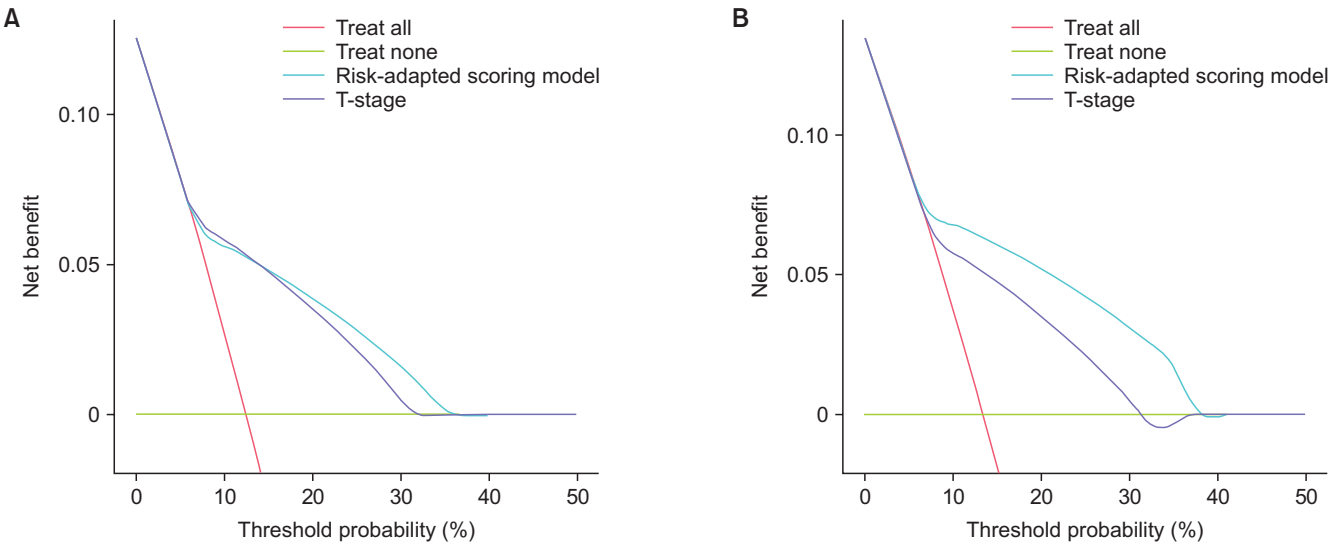

Fig. 2. Decision curve analysis comparing the risk-adapted scoring model and T stage in the prediction of disease recurrence. Decision curve analysis for the probability of 5-year recurrence-free survival (A) and 7-year recurrence-free survival (B).

a worse prognosis.

This multicenter study has several limitations owing to its observational design. First, the current study is still limited by its retrospective study design and small sample size. Given the low prevalence of UTUC and strict inclusion criteria for localized UTUC with ≤pT2, analyses with additional patients were limited. Second, this model has limited use when performing risk-adjusted scoring for UTUC patients with >pT3 disease. Considering that the POUT trial clearly demonstrated the clinical benefit of AC in pT3 or locally advanced disease, we did not develop the model for diseases higher than pT2. Finally, molecular biomarkers (e.g., PD-1 or PD-L1 expression), liquid biopsy results, and tumor mutational burden were not included as risk factors in this study, although they may act as important prognostic factors in management of UTUC.

CONCLUSIONS

We present a risk-adapted scoring model to predict the risk of recurrence in patients with non-metastatic UTUC with ≤pT2 disease. The results of this multicenter study demonstrated that our risk-adapted scoring model may be superior to pathologic tumor staging alone in selecting patients with non-metastatic UTUC with ≤pT2 who would ideally benefit from AC after RNU. Our results suggest that AC should be considered for patients in the high-risk group given their poor survival outcomes.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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SUPPLEMENTARY MATERIAL

Supplementary material can be found via https://doi.org/10.4111/icu.20240323.

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