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Risk-adapted scoring model to identify candidates benefiting from adjuvant chemotherapy after radical nephroureterectomy in nonmetastatic upper tract urothelial carcinoma with ≤pT2

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Introduction After radical nephroureterectomy (RNU), adjuvant chemotherapy (AC) is recommended in either muscle invasive or lymph node positive upper urinary tract urothelial carcinoma (UTUC). However, optimal patient selection remains to be studied. We propose a risk-adapted scoring model for selecting patients for AC in localised UTUC with ≤pT2.

Material and methods The model was based on 7 risk factors modified from the risk stratification system in the European Association of Urology guideline for localised UTUC. Each risk factor indicated one point; total scores were used to categorise patients as at low or high risk for disease recurrence. We applied our model to 135 patients with localised UTUC with ≤pT2, who underwent RNU without AC. Recurrence-free survival and cancer-specific survival were analysed based on risk group.

Results A risk score of ≥4 points indicated high risk (33/135 patients [24.4%]). The accuracy of predicting recurrence was 82.9% (95% confidence interval [CI]: 75.5–88.9%) with a negative predictive value of 93.1% (95% CI: 87.9–96.2%). Disease recurred in 51.5% of high-risk patients and 6.9% of low-risk patients. Multivariate analysis indicated that high-risk was independently associated with recurrence and cancer-specific death (hazard ratio [HR] = 10.20, 95% CI: 3.94–26.44%, HR = 8.72, 95% CI: 2.47–30.73%, all p <0.001, respectively).

Conclusions The risk-adapted scoring model might be an effective way for selecting patients who may benefit from AC after RNU in nonmetastatic UTUC with ≤pT2. These results should be validated in a larger, prospective study.

Key Words: nephroureterectomy ‹› upper urinary tract ‹› chemotherapy ‹› adjuvant ‹› risk-adapted scoring model

INTRODUCTION

Upper tract urothelial carcinoma (UTUC) is a rare disease, accounting for ≤5% of all of urothelial tumours [1]. Standard treatment for nonmetastatic UTUC is radical nephroureterectomy (RNU) with bladder cuff resection [2, 3]. However, approximately 25% of patients with UTUC experience disease recurrence or metastasis after RNU, and cancer-specific mortality after recurrence or metastasis remains poor [4]. Although many studies and much effort over the past decades has demonstrated the efficacy of perioperative chemotherapy for improving UTUC prognosis, the efficacy of perioperative systemic therapy remains inconclusive. Recently, the results of a phase 3 randomised controlled trial (the POUT trial) on the efficacy of adjuvant chemotherapy (AC) after RNU showed significant

improvement in disease-free survival among patients with locally advanced UTUC [5]. Based on the results of the POUT trial, the current European Association of Urology (EAU) guidelines for UTUC recommend adjuvant platinum-based chemotherapy after RNU for patients with pT2–T4 and/or pN+ UTUC [3].
The POUT trial indicated that AC had greatly affected disease-free and metastasis-free survival; however, chemotherapy induced acute toxicity, and a transient negative impact on patient-reported quality of life was reported [5]. Furthermore, the benefit of AC in pT2 UTUC was not greater than in locally advanced UTUC. Thus, administering systemic therapy to all patients with pT2 disease with a low risk of recurrence would not avoid the possibility of overtreatment. In addition, although individuals with pT1 disease are not candidates for AC based on the study results, previous studies have reported frequent disease recurrences [4, 6].
Because of the heterogeneous nature of UTUC and the risk of overtreatment with AC, there is a need to develop an accurate postoperative risk stratification model based on real-world data for appropriate decision-making and patient counselling in AC. In this study, we aimed to present a risk-adapted scoring model for screening candidates for AC in nonmetastatic UTUC with ≤pT2.

MATERIAL AND METHODS

Patients

We retrospectively identified 198 patients who underwent RNU for UTUC between January 2010 and June 2020 at Inje University Busan Paik Hospital, Republic of Korea. Study inclusion criteria were as follows: (1) pathologic diagnosis of urothelial carcinoma (UC) in renal pelvic or ureter, (2) pathologic tumour 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. Exclusion criteria were as follows: (1) patients with previous or sequential second primary cancers (except for bladder tumour), (2) nonRNU, and (3) patients who received perioperative neoadjuvant or adjuvant systemic therapy. Ultimately, we analysed 135 patients with pTa-2N0M0 UTUC following RNU in this study. Based on the surgeon's preference, the open, laparoscopic, or robotic approach was used for RNU with bladder cuff resection. The bladder cuff resection was performed through the extravesical approach [7]. Lymphadenectomy was not routinely performed, except in patients with suspiciously enlarged lymph nodes in preoperative imaging or in cases with suspicious intraoperative findings at the surgeon's discretion. Patients were generally followed up every 3 months in the first year after RNU, every 6 months in years 2–5, and annually afterward. Follow-up evaluations included serum laboratory tests, cystoscopy, and regular thoracoabdominal computed tomography scan or magnetic resonance imaging. Disease recurrence was defined as a new >10-mm lesion previously undetected by radiologic evaluation in the locoregional surgical field or outside the urinary tract. Intravesical recurrence was not considered to indicate disease recurrence.
We collected data on age, gender, tumour size and multifocality, computed tomography urography (CTU) invasion, preoperative hydronephrosis, pathologic tumour staging and grading, presence of variant histology, and status of disease recurrence. CTU invasion was defined as infiltration into renal parenchyma, renal sinus fat, or periureteric tissue identified on cross-sectional imaging [8]. Preoperative hydronephrosis was determined from preoperative radiologic reports of upper tract imaging including CTU and magnetic resonance imaging.

Pathologic evaluation

A genitourinary pathologist with >15 years of experience at our institution histologically confirmed all specimens. Tumour staging was assessed according to the seventh and eighth American Joint Committee on Cancer tumour, node, metastasis classification system and graded according to the 2004 and 2016 World Health Organisation (WHO) system and the International Society of Urological Pathology consensus classification [9–12]. Variant histology was assessed based on a previously reported reference well accepted by the uropathological community and the WHO system [9, 11, 13]. Tumour size was measured based on the largest dimension determined by macroscopic and microscopic examinations of single tumour frozen sections. We defined tumour location as the renal pelvis, ureter, or both the renal pelvis and the ureter. Tumour multifocality was defined as pathologic confirmation of the synchronous presence of tumours in any location in the renal pelvis and ureter. In cases in which tumour multifocality was present, we obtained the largest tumour diameter for analysis. We also evaluated concomitant carcinoma in situ and lymphovascular invasion (LVI) status.

Risk-adapted scoring model for adjuvant systemic therapy after radical nephroureterectomy in nonmetastatic upper tract urothelial carcinoma

We propose a risk-adapted scoring model to identify patients who would benefit from adjuvant sys-

temic therapy in nonmetastatic UTUC (Table 1). This model consists of 7 risk factors: (1) high-grade tumour; (2) tumour size ≥2 cm, (3) multifocal disease, (4) local invasion on CTU, (5) hydronephrosis, (6) previous history for bladder UC, and (7) variant histology. Among the 7 risk factors, we proposed the use of 6 clinicopathologic factors as risk factors in the risk stratification model for nonmetastatic UTUC in the EAU guideline [3]; one risk factor was modified from "Previous radical cystectomy for high-grade bladder cancer" to "History of bladder UC". Each criterion corresponds to one point, and the combined score of all criteria was used to categorise patients as having low or high risk of disease recurrence.

Statistical analysis

Continuous variables are presented as means with standard deviations or medians with interquartile range (IQR). Categorical variables are presented as frequency with percentage. We compared the clinicopathologic factors affecting disease recurrence and survival using the χ^2-test, Fisher's exact test, and linear-by-linear association for categorical data; for continuous variables, we used Student's t test and one-way analysis of variance. We adopted the maximal chi-square method to determine which cutoff of risk scores in each data set best categorised patients into subgroups of low and high risk of disease recurrence (based on the likelihood of survival), with the log-rank test used as the method for measuring the grouping strength [14, 15]. For each of the high-risk cutoff thresholds, we tested univariable sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and predicting accuracy for disease recurrence after RNU. Accuracy was defined by area under the receiver-operating characteristics (AUC ROC) curve. We estimated the prognostic effects of clinicopathologic variables on disease recurrence and survival using univariate and multivariate Cox proportional hazards regression models. Hazard ratios (HRs) with 95% confidence intervals (CIs) were used to assess the strength of the individual 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. We performed statistical analyses using SPSS V27.0 (IBM Corp, Armonk, NY, USA), MedCalc V22.0 (MedCalc Software Ltd, Ostend, Belgium), or Maxstat, a maximal χ^2-test method in R statistical package 2.13.0 (R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org). All tests were two-sided, and $p < 0.05$ was considered statistically significant.

Table 1. *Risk-adapted scoring model for adjuvant systemic therapy in nonmetastatic UTUC with ≤pT2*

Risk factors (1 point for each factor)	Score
High-grade tumour	1 point
Tumour size ≥ 2 cm	1 point
Multifocal disease	1 point
Local invasion on CTU	1 point
Hydronephrosis	1 point
Previous history for bladder urothelial carcinoma	1 point
Variant histology	1 point
Risk group	**Sum of scores**
Low risk of disease recurrence	0~3 points
High risk of disease recurrence	≥ 4 points

CTU – computed tomography urography

Bioethical standards

This single-centre study was approved by the Medical Ethics Committee of the Inje University Busan Paik Hospital (BPIRB 2023-04-014) and was in complete agreement with the Declaration of Helsinki.

RESULTS

Overall, we included 135 patients with nonmetastatic UTUC with ≤pT2 (pT2: 30 patients [22.2%]; ≤pT1: 105 patients [77.8%]) who underwent RNU. The median follow-up period was 35.2 months (4.9–138 months), and 21 patients (15.6%) had died at the time of analysis. Table 2 displays the clinicopathologic characteristics stratified by risk factor scores. Sixty-seven (49.6%) patients had 2 or fewer risk factors, 35 (25.9%) had 3 risk factors, and 33 (24.4%) had more than 4 risk factors. The incidence of ≥pT2 disease was 10.4% in patients with 2 or fewer risk factors, 28.6% in patients with 3 risk factors, and 39.4% in patient with 4 or more risk factors. Patients with 4 or more risk factors showed higher rates of positive results in all 7 risk factors than patients with 3 or fewer risk factors ($p < 0.05$).

Using the maximal χ^2-test method, we found that segregation was best achieved using a risk score cutoff value of 3 points. Using this criterion, Table 3 shows the performance of the risk score thresholds for predicting disease recurrence and cancer-specific death using the univariable tests. The accuracies for recurrence prediction of the high-risk cutoff value of ≥3 points and ≥4 points were 61.5% (95% CI: 52.7–69.7%) and 82.9% (95% CI: 75.5–88.9%), respectively. In the univariate analysis, ≥pT2, high-

Table 2. *Clinicopathologic characteristics stratified by risk factor scores*

Characteristics	Summed risk scores				p-value
	Score ≤2 (n = 67)	Score = 3 (n = 35)	Score ≥4 (n = 33)	Total (n = 135)	
Age, years, median (IQR)	69 (46–86)	72 (42–85)	73 (53–83)	71 (45–86)	0.290
Sex, n (%)					
Male	52 (77.6)	24 (68.6)	19 (57.6)	95 (70.4)	0.115
Female	15 (22.4)	11 (31.4)	14 (42.4)	40 (29.6)	
BMI, kg/m^2, median (IQR)	24.6 (18.5–29.7)	24.1 (18.4–27.5)	23.6 (18.6–30.4)	24.2 (18.4–30.3)	0.603
Diabetes mellitus, n (%)					
Absent	53 (79.1)	28 (80.0)	22 (66.7)	103 (76.3)	0.325
Present	14 (20.9)	7 (20.0)	11 (33.3)	32 (23.7)	
Hypertension, n (%)					
Absent	34 (50.7)	18 (51.4)	15 (45.5)	67 (49.6)	0.857
Present	33 (49.3)	17 (48.6)	18 (54.5)	68 (50.4)	
ECOG performance status, n (%)					
0–1	63 (94.0)	29 (82.9)	31 (93.9)	123 (91.1)	0.137
≥2	4 (6.0)	6 (17.1)	2 (6.1)	12 (8.9)	
History of bladder urothelial carcinoma, n (%)					
Absent	65 (97.0)	33 (94.3)	25 (75.8)	123 (91.1)	0.001
Present	2 (3.0)	2 (5.7)	8 (24.2)	12 (8.9)	
Hydronephrosis, n (%)					
Absent	51 (76.1)	7 (20.0)	4 (12.1)	62 (45.9)	<0.001
Present	16 (23.9)	28 (80.0)	29 (87.9)	73 (54.1)	
CTU invasion, n (%)					
Absent	64 (95.5)	30 (85.7)	10 (30.3)	104 (77.0)	<0.001
Present	3 (4.5)	5 (14.3)	23 (69.7)	31 (23.0)	
Operation method, n (%)					
Open	13 (19.4)	14 (40.0)	10 (30.3)	37 (27.4)	0.208
Laparoscopic	38 (56.7)	17 (48.6)	17 (51.5)	72 (53.3)	
Robotic	16 (23.9)	4 (11.4)	6 (18.2)	26 (19.3)	
LN dissection, n (%)					
No	66 (98.5)	31 (88.6)	28 (84.8)	125 (92.6)	0.010
Yes	1 (1.5)	4 (11.4)	5 (15.2)	10 (7.4)	
Tumour location, n (%)					
Pelvic-caliceal	46 (68.7)	11 (31.4)	6 (18.2)	63 (46.7)	<0.001
Ureter	19 (28.3)	22 (62.9)	16 (48.5)	57 (42.2)	
Both	2 (3.0)	2 (5.7)	11 (33.3)	15 (11.1)	
Tumour size, cm, median (IQR)	2.5 (0.8–7.0)	2.5 (1.0–6.0)	3.5 (1.5–7.7)	2.8 (0.8–6.5)	0.037
Multifocality, n (%)					
Absent	64 (95.5)	27 (77.1)	13 (39.4)	104 (77.0)	<0.001
Present	3 (4.5)	8 (22.9)	20 (60.6)	31 (23.0)	
Pathologic staging, n (%)					
Ta/Tis/T1	60 (89.6)	25 (71.4)	20 (60.6)	105 (77.8)	0.003
T2	7 (10.4)	10 (28.6)	13 (39.4)	30 (22.2)	
Pathologic grading, n (%)					
Low-grade	38 (56.7)	6 (17.1)	3 (9.1)	47 (34.8)	<0.001
High-grade	29 (43.3)	29 (82.9)	30 (90.9)	88 (65.2)	
Variant histology, n (%)					
Absent	65 (97.0)	29 (82.9)	27 (81.8)	121 (89.6)	0.010
Present	2 (3.0)	6 (17.1)	6 (18.2)	14 (10.4)	
Lymphovascular invasion, n (%)					
Absent	66 (98.5)	35 (100)	32 (97.0)	133 (98.5)	0.664
Present	1 (1.5)	0 (0)	1 (3.0)	2 (1.5)	
Tumour necrosis, n (%)					
Absent	66 (98.5)	33 (94.3)	32 (97.0)	131 (97.0)	0.536
Present	1 (1.5)	2 (5.7)	1 (3.0)	4 (3.0)	
Concomitant CIS, n (%)					
Absent	62 (92.5)	25 (71.4)	21 (63.6)	108 (80.0)	0.001
Present	5 (7.5)	10 (28.6)	12 (36.4)	27 (20.0)	
Synchronous bladder tumour, n (%)					
Absent	57 (85.1)	26 (74.3)	25 (75.8)	108 (80.0)	0.339
Present	10 (14.9)	9 (25.7)	8 (24.2)	27 (20.0)	
Positive ureteral resection margin, n (%)					
Absent	63 (94.0)	33 (94.3)	28 (84.8)	124 (91.9)	0.151
Present	4 (6.0)	2 (5.7)	5 (15.2)	11 (8.1)	

BMI – body mass index; CIS – carcinoma in situ; CTU – computed tomography urography; ECOG – Eastern Cooperative Oncology Group; IQR – interquartile range; LN – lymph node; n – number of patients

Table 3. *Performance of different risk score cutoffs for prediction of recurrence in 135 patients treated with RNU*

Risk scores cutoff for high-risk group	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	PLR (95% CI)	NLR (95% CI)	Accuracy % (95% CI)	AUC %
≥3 points	83.3 (62.6–95.3)	56.8 (47.0–66.1)	29.4 (23.9–35.5)	94.0 (86.4–97.5)	1.9 (1.4–2.5)	0.3 (0.1–0.7)	61.5 (52.7–69.7)	70.0
≥4 points	70.8 (48.9–87.4)	85.6 (77.6–91.5)	51.5 (38.7–64.1)	93.1 (87.9–96.2)	4.9 (2.9–8.2)	0.3 (0.2–0.6)	82.9 (75.5–88.9)	78.2

AUC – area under the curve; CI – confidence interval; NLR – negative likelihood ratio; NPV – negative predictive value; PLR – positive likelihood ratio; PPV – positive predictive value

grade tumour, multifocal disease, CTU invasion, and a high-risk cutoff value of ≥3 points and ≥4 points were significant poor prognostic factors for disease recurrence (all p <0.05). Advanced age, history of bladder UC, CTU invasion, and a high-risk cutoff value of ≥3 and ≥4 were significant poor prognostic factors for caner-specific death (all p < 0.05) (Table 4). In the multivariable models that adjusted for the effects of preoperative clinicopathologic features, both a high-risk cutoff value of ≥3 points (HR = 3.98; 95% CI: 1.31–12.11, p = 0.015) and ≥4 points (HR = 10.20, 95% CI: 3.94–26.44, p <0.001) were independently associated with disease recurrence after RNU. However, only a high-risk cutoff value of ≥4 points (HR = 8.72, 95% CI: 2.47–30.73, p <0.001) was associated with cancer-specific death (Table 5).

Overall, 24 (17.8%) patients experienced disease recurrence. Ten of 30 (33.3%) patients with pT2 and 14 of 105 (13.3%) patients with ≤pT1 experienced disease recurrence. When we adopted a high-risk cutoff value as ≥4 points, 17 of 33 (51.5%) high-risk patients and 7 of 102 (6.9%) low-risk patients experienced disease recurrence. The high-risk group showed poorer RFS than the low-risk group (median, 37.6 months, 95% CI: 14.5–70.5 months vs not reached; HR = 26.53, 95% CI: 9.62–73.14, p < 0.001), and the probability of RFS at 24 months was 62.0% (95% CI: 54.3–70.6%) and 94.4% (95% CI: 91.8–96.7%), respectively (Figure 1A). Similarly, the high-risk group showed poorer CSS than the low-risk group (median, 61.6 months, 95% CI: 40.1–61.6 months vs not reached; HR = 18.89, 95% CI: 4.56–78.27, p <0.001), and the probability of CSS at 24 months was 90.1% (95% CI: 84.7–94.6%) and 97.4% (95% CI: 95.5–98.2%), respectively (Figure 1B).

DISCUSSION

In this study, we aimed to establish and validate a simple risk stratification model for determining

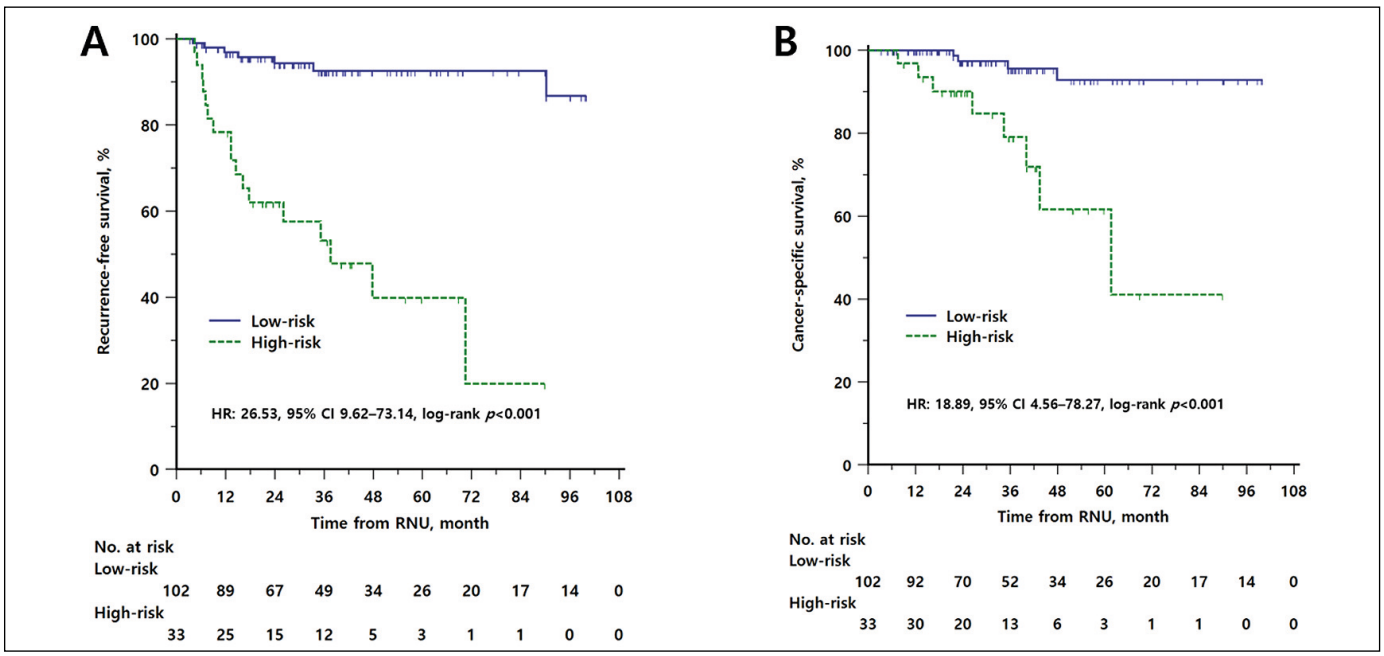

Figure 1. A) *Kaplan-Meier survival curves for recurrence-free survival.* **B)** *Cancer-specific survival stratified according to risk groups (defined by summed scores).*

Table 4. *Univariable Cox proportional hazard analysis for recurrence-free and cancer-specific survival in 135 patients treated with RNU*

Parameter	Recurrence-free survival		Cancer-specific survival	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.03 (0.98–1.07)	0.172	1.08 (1.01–1.17)	0.021
Gender (female)	1.15 (0.47–2.81)	0.755	0.93 (0.25–3.46)	0.918
Synchronous bladder tumor	2.31 (0.98–5.47)	0.057	2.39 (0.71–8.01)	0.158
Concomitant carcinoma in situ	0.82 (0.28–2.40)	0.716	0.91 (0.19–4.21)	0.910
Lymphovascular invasion	1.13(0.15-7.35)	0.956	1.23 (0.32–6.48)	0.973
Tumor necrosis	1.25 (0.17–9.33)	0.823	1.38 (0.23–10.36)	0.968
Positive ureteral resection margin	2.39 (0.82–7.01)	0.112	3.63 (0.98–13.44)	0.053
T stage pTa/Tis/T1 pT2	1 3.23 (1.42–7.31)	0.005	1 1.43 (0.38–5.29)	0.592
Risk factors for adjuvant systemic therapy High-grade	3.23 (1.10–9.51)	0.033	3.40 (0.74–15.63)	0.115
History of bladder urothelial carcinoma	2.33 (0.79–6.84)	0.122	6.24 (1.86–20.94)	0.003
Tumor size (≥2 cm)	3.48 (0.82–14.85)	0.091	3.06 (0.39–23.84)	0.284
Multifocality	3.45 (1.55–7.71)	0.003	2.45 (0.77–7.78)	0.127
Variant histology	2.05 (0.69–6.01)	0.193	2.38 (0.52–10.98)	0.265
CTU invasion	8.43 (3.07–32.51)	<0.001	9.56 (3.84–40.27)	<0.001
Hydronephrosis	2.00 (0.83–4.82)	0.123	1.53 (0.46–5.09)	0.488
Risk scores cutoff: 2 points ≤2 points (low-risk) ≥3 points (high-risk)	1 4.96 (1.69–14.50)	0.004	1 5.03 (1.10–22.99)	0.037
Risk scores cutoff: 3 points ≤3 points (low-risk) ≥4 points (high-risk)	1 11.24 (4.39–28.69)	<0.001	1 8.29 (2.46–27.93)	<0.001

Table 5. *Multivariable Cox proportional hazard analysis for recurrence-free and cancer-specific survival in 135 patients treated with RNU*

Risk Scores Cutoff for high-risk group	Recurrence-free survival		Cancer-specific survival	
	HR (95% CI)	p-value	HR (95% CI)	p-value
≥3 points	3.98 (1.31–12.11)	0.015	3.98 (0.85–18.71)	0.079
≥4 points	10.20 (3.94–26.44)	<0.001	8.72 (2.47–30.73)	<0.001

The multivariable base models in addition to age (recurrence-free survival) and tumour stage (cancer-specific survival)

adjuvant systemic therapy use after RNU in patients with nonmetastatic UTUC with ≤ pT2 disease. Our study demonstrated that, regardless of pathologic tumour stage, high-risk patients in our model are at increased risk of recurrence after RNU and are candidates for AC.

Several retrospective studies have examined the benefit of AC for improving the oncologic outcomes in patients with UTUC after RNU [16–18]. Most of these focused on the efficacy of AC in UTUC with advanced tumour stage (≥pT3) or locoregional lymph node positive disease. Despite the positive results for RFS and CSS shown in these retrospective studies of AC, there was no clear recommendation on the use of adjuvant systemic therapy for treating of UTUC over the long term. Fortunately, a randomised phase 3 trial on AC in advanced UTUC, the POUT trial, has been reported [5]. A total of 261 patients who underwent RNU for pT2-T4N0-3M0 UTUC were randomised to 4 cycles of AC or observation. The authors found a significant difference in disease-free survival at 2 years in favour of chemotherapy (51% vs 70%). The POUT trial underlines the benefit of adjuvant platinum-based chemotherapy for patients who underwent RNU for locally advanced or lymphatic metastasised UTUC. Based on the POUT trial, current guidelines recommend adjuvant platinum-based chemotherapy for pT2-T4 or N+ UTUC after RNU [2, 3]. However, in the subgroup analysis, we observed a statistically significant disease-free survival benefit from AC not in pT2 disease but only in pT3/4 disease. This suggests that all patients with pT2 disease might be at risk for overtreatment with adjuvant systemic therapy. In addition, although an increasing pathologic tumour stage increases the risk of disease recurrence and metastasis, in real-world clinical practice, patients with pT1 UTUC often experience disease recurrence or metastasis [19]. Therefore, to avoid the risk of undertreatment in patients with high-risk UTUC, not only the pathologic tumour stage but also other clinicopathologic factors should be considered. Thus, identifying appropriate candidates who may

benefit from adjuvant systemic therapy after RNU is of paramount importance.

To provide more effective evidence-based treatment, international guidelines have recommended risk stratification for other urological cancers, such as prostate cancer and renal cell carcinoma. The EAU also developed a risk stratification system for UTUC. This system is useful for risk-stratifying UTUC between low- and high-risk tumours to identify patients who are more suitable for kidney-sparing surgery rather than RNU. In other words, the EAU UTUC risk stratification system is not a tool for selecting patients for AC. Although the EAU guideline recommends AC in high-risk UTUC using prognostic nomograms, this process has limitations in clinical use due to the complexity and diversity of nomograms.

In this regard, by adopting and modifying the risk stratification model for nonmetastatic UTUC in the EAU guideline, we developed and proposed a simple risk-adapted scoring model for adjuvant systemic therapy in patients with localised UTUC with ≤pT2. The risk stratification model in the EAU guideline consisted of 8 risk factors: multifocal disease, tumour >2 cm, high-grade cytology, high-grade in ureterorenoscope (URS) biopsy, CTU invasion, hydronephrosis, previous radical cystectomy for high-grade bladder cancer, and variant histology. Among the 8 risk factors, we combined "High-grade in URS biopsy" and "High-grade cytology" into "High-grade tumour" in this study because the final pathologic inspection after RNU was determined to be a more accurate and important factor in clinical practice. The biggest difference from the original model is the change of "Previous radical cystectomy for high-grade bladder cancer" to "History of bladder UC". Although there might be controversy about this content, a recent Surveillance, Epidemiology, and End Results registry-based study showed that UTUC in patients with a previous or simultaneous bladder cancer history, regardless of tumour grade and stage, had a significantly adverse effect on UTUC prognosis [20]. In addition, we also considered the incidence of UTUC in association with bladder cancer. The incidence of UTUC after radical cystectomy ranged from 0.75% to 6.4% [21, 22]. However, approximately 25% of UTUC patients had a history of non-muscle invasive bladder cancer at time of diagnosis or treatment with RNU [4, 23]. Other factors, including tumour size, multifocality, CTU invasion, hydronephrosis, and variant histology, have been reported to influence the prognosis of UTUC and were used as the main risk factors in our model [24–27]. Indeed, we also observed an increased RFS and CSS risk in patients who were positive for these factors.

Of the multiple pathologic factors, only variant histology and grade were included in the risk-adapted scoring model. We did not include pathologic tumour stage as a risk factor because our model is designed to prevent overtreatment at pT2 and to pre-screen those who need adjuvant treatment in ≤pT1 patients. In addition, although LVI is a well-known factor that influences disease recurrence and progression in UTUC [26], it did not appear to be an influential factor in both RFS and CSS in our cohort. It is probably because only 2 (1.5%) of the patients included in this study were LVI positive. This should be explored in further research in a larger cohort.

We found that a high-risk cutoff value of ≥4 points was best for identifying disease recurrence. Although sensitivity and NPV were higher for the ≥3-point cutoff value, the ≥4-point cutoff value provided better specificity, PPV, accuracy, and AUC ROC. In addition to the diagnostic tests indicating the superior performance of the ≥4-point cutoff value, multivariable analysis showed that both RFS and CSS were significant when adopting ≥4 points as the distinguishable cutoff value between the low- and high-risk groups.

In this study, 33.3% of pT2 patients and 13.3% of ≤pT1 patients experienced disease recurrence. If AC candidates were selected based solely on pathologic tumour stage, as proposed by the POUT trial, more than half of the pT2 patients would be at risk of overtreatment and more than 10% of the ≤pT1 patients would be at risk of undertreatment. In addition, we observed a significant increase in the proportion of pT2 disease in the high-risk group. This finding suggests that, even though tumour stage was not considered as a risk factor in identifying candidates for AC, our risk-adapted scoring model could help decision-making in pursuit of tailored individual patient care by selecting patients with pT2 who might have a worse prognosis.

This study has several limitations. First, the retrospective study design is associated with an inherent potential for selection bias. Second, this scoring system is limited in its use of risk-adjusted scoring for ≥pT3 disease. As shown by the POUT trial, there is a clear benefit of adjuvant treatment in pT3 or locally advanced disease, so we did not develop this model for these patients. Third, we did not include other molecular biomarkers, such as PD-1 or PD-L1 expression, liquid biopsy results, and tumour mutational burden, as risk factor in this study. Although these molecular biomarkers are significantly associated with worse prognosis or systemic therapy response [28], we did not include them as risk factors because the purpose of this study is to develop a risk-scoring model that can be easily

used in clinical practice. Finally, due to the small number of patients and events, the statistical power might be limited. Therefore, further research in a larger cohort is needed to confirm our findings.

CONCLUSIONS

We presented a risk-adapted scoring model that might be a better indicator of disease recurrence in patients with nonmetastatic UTUC with ≤pT2. Further studies with larger cohorts are needed to validate the risk-adapted scoring model, which may allow more precise identification of ideal candidates for AC after RNU among patients with nonmetastatic UTUC with ≤pT2.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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ETHICS APPROVAL

All included patients undergoing radical treatment provided written informed consent for surgery. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Medical Ethics Committee of the Inje University Busan Paik Hospital (BPIRB 2023-04-014).

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