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Postoperative Nomogram for Predicting Relapse-Free Survival after Radical Nephroureterectomy Combined with Chemotherapy in Patients with Upper Tract Urothelial Carcinoma

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Abstract

Objective: To identify the risk factors for recurrence and establish a nomogram to predict Relapse-Free Survival (RFS) in patients with Upper Tract Urothelial Carcinoma (UTUC) after Radical Nephroureterectomy (RNU) combined with chemotherapy.

Methods: A retrospective analysis was conducted to identify the risk factors for recurrence of the 101 UTUC patients who underwent RNU and bladder cuff resection combined with chemotherapy. Overall Survival (OS) and RFS were assessed using the Kaplan-Meier method. Cox regression model was used to identify risk factors for survival outcomes. The nomogram was developed to predict RFS at 1, 3 and 5-years, after RNU combined with chemotherapy. The performance of the nomogram was evaluated by the concordance index (C-index) and the Receiver Operating Characteristic (ROC) curve.

Results: Of the 101 UTUC patients, 40 (39.6%) experienced tumor recurrence, including 32 at bladder and 8 at the contralateral upper urinary tract. The multivariate Cox regression analysis showed that hydronephrosis, T stage, Neoadjuvant Chemotherapy (NAC), chemotherapy cycle and Lymphovascular Invasion (LVI) were the independent risk factors for UTUC recurrence. A nomogram was developed by employing these five predictive factors. For RFS predictions, the C-index value of the nomogram was 0.791. The areas under the curve (AUCROC) of the nomogram were 0.853, 0.893 and 0.903 respectively.

Conclusion: Hydronephrosis, T stage, NAC, chemotherapy cycle and LVI are shown to be independent factors for affecting the recurrence of UTUC patients. The nomogram is a simple-to-use tool for physicians to facilitate postoperative personalized prognostic evaluation and determine therapeutic strategies for UTUC patients.

Keywords: Upper tract urothelial carcinoma; Radical nephroureterectomy; Intravenous chemotherapy; Recurrence; Nomogram

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Introduction

Urothelial Carcinoma (UC) is the second most common genitourinary malignancy worldwide. The Lower Tract Urothelial Carcinoma (LTUC) is the most common type and accounts for over 90% of UC. The Upper Tract Urothelial Carcinoma (UTUC) is rare and accounts for about 5% to 10% of UC and its annual incidence is 2/100,000 persons [1]. UTUC is an aggressive malignancy with high local recurrence rate and distant metastasis rate. The 5-year Cancer-Specific Survival (CSS) rate is less than 50% for pT2/pT3 and less than 10% for pT4 UTUC patients [2]. Due to the invasiveness and delayed diagnosis of UTUC, about 35% of the patients have reached T3 stage or had lymph node involvement when they accept the Radical Nephroureterectomy (RNU) [3]. Even though they accepted surgical intervention, the 5-year CSS is still less than 45% in pT3 stage patients and less than 35% in lymph node positive patients [4]. The recurrence rate is high after surgery, including Intravesical Recurrence (IVR), contralateral upper urinary tract and local retroperitoneal recurrence. IVR is the most common type and accounts for 22% to 47% [5]. Therefore, RNU alone is not enough to improve outcomes for UTUC patients. At present, there were some reports on Adjuvant Chemotherapy (AC) for UTUC at home and abroad. However, it is still controversial

whether AC could improve Relapse-Free Survival (RFS) of UTUC patients [6,7]. In addition, there is no research that has focused on risk factors for recurrence in UTUC patients underwent RNU combined with chemotherapy. The purpose of this study is to identify the risk factors of tumor recurrence and to establish a nomogram for predicting RFS in patients with UTUC after RNU combined with intravenous chemotherapy.

Patients and Methods

Study population

This study utilized the UTUC database of the Department of Urology of Beijing Friendship Hospital affiliated to Capital Medical University from 2013 to 2019, with approval from the Institutional Review Board for the Protection of Human Subjects. Inclusion criteria: 1) The treatment regimen is RNU and bladder cuff resection combined with Gemcitabine + Cisplatin (GC) intravenous chemotherapy; 2) Postoperative pathology ≥ pT1, no lymph node metastasis and no distant metastasis; 3) Complete clinical data; 4) The tumor grade is high-grade; 5) The baseline renal function was normal; 6) The margin status is negative. Exclusion criteria: 1) LTUC or other malignant tumors; 2) Death within 30 days after surgery. A total of 101 patients were enrolled according to the above criteria. The clinicopathologic characteristics of patients were recorded as follows: gender (male and female), age at diagnosis, hydronephrosis (negative and positive), tumor location (renal pelvis, ureter and multifocal lesion), tumor side (left and right), T stage (T1,T2,T3 and T4), Lymph Node Dissections (LND) (yes and no), Neoadjuvant Chemotherapy (NAC) (negative and positive), chemotherapy cycle (1 to 2 and 3 to 4) and Lymphovascular Invasion (LVI) (negative and positive). RNU pathologies were reviewed by staff pathologists with expertise in genitourinary pathology for T stage, tumor grade, and presence of LVI. UTUC was staged based on the criteria listed in the AJCC staging manual, 7th edition. Tumor grade was determined using the 2004 World Health Organization grading system. LVI was described as the presence of tumor cells that were nested within an endothelium-lined space and the absence of underlying muscular walls [8]. All received GC intravenous chemotherapy within 90 days after surgery. In all patients receiving AC, 19 patients underwent GC regimens NAC before surgery, usually 2 cycles. All patients undergo ureteroscopic biopsy prior to initiation of NAC. Written informed consent was provided by all participations.

Therapy methods

Radical surgery was performed by urologists according to the standard criteria for RNU with bladder cuff removal. All participants underwent laparoscopic or open radical surgery. LND were performed in an extended or limited manner with the urologists' discretion. After stitches removed, each patient was reevaluated by the chest radiograph, blood routine, liver function, kidney function and other biochemical indicators. When the most biochemical indicators such as liver and kidney function returned to normal or preoperative levels and patients had no indications of infection, anemia and bleeding, systemic AC with standard GC regimens was performed. Gemcitabine (1000 mg/m^2) was given on days 1, 8 and 15 of each cycle and cisplatin (70 mg/m^2) was given on days 2 of each cycle. The chemotherapy plan took 28 days as one cycle. Protocol-specified recommendations were for chemotherapy to begin within 90 days of RNU combined with bladder cuff resection, for gemcitabine to be given as a 30-min intravenous infusion in 500 mL normal saline and cisplatin to be given as a 2-h intravenous infusion in 1 L saline. The implementation of NAC regimen was the same as postoperative AC. During chemotherapy, the patients were given acid inhibition, hydration, antiemetic and other auxiliary treatment. All patients had no obvious abnormality in routine assessment before chemotherapy.

Follow-up

This research was a retrospective study, and no standardized follow-up was employed. Generally, the patient underwent clinical and radiological follow-up postoperatively following routine institutional protocol. All patients in this study were examined by blood routine, liver and kidney function, abdominal ultrasound, chest radiograph every six months. The abdominal CT was performed by every year and the cystoscopy was performed by every 3 months for the first 2 years, every 6 months thereafter. The endpoints included Recurrence-Free Survival (RFS) and Overall Survival (OS) relative to the time of treatment initiation.

Statistical analysis

Statistical analyses were performed by SPSS software for windows (version 23.0). Variables were expressed in counts and percentages. RFS and OS were calculated using the Kaplan-Meier approach with a log-rank test. The Chi-square test and Fisher's exact test were employed in univariate analysis to assess the relationships between each clinicopathologic characteristic and UTUC recurrence. Then, predictors with $P<0.05$ were included in multivariate Cox proportional-hazards model. Subsequently, a nomogram model was developed based on significant predictive factors in multivariate Cox regression analysis using R software (version 3.6.3). Approximately 500 bootstrap re-samples were employed for internal validation. The concordance index (C-index) and calibration plots were used to assess nomogram performance. The predictive accuracy of the nomogram model at RFS of 1, 3 and 5-years was calculated using the Receiver Operating Characteristic (ROC) curve. Differences were deemed statistically significant at $P<0.05$.

Results

Clinicopathological characteristics and follow-up results of participants

A total of 101 patients were enrolled including 29 cases of renal pelvis carcinoma, 56 cases of ureteral carcinoma and 16 cases of renal pelvis carcinoma complicated with ureteral carcinoma. The clinical characteristics of patients are illustrated in Table 1. The cohort included 55 men and 46 women with a median age of 65 years (IQR: 55 to 78 years). The median follow-up time was 22 months (range: 2 to 82 months). There were 40 patients with recurrence, including 32 patients at bladder and 8 patients at the contralateral upper urinary tract. The OS of patients at 1, 3 and 5-years were 82.1%, 68.9% and 42.1% and the RFS of patients were 78.3%, 54.2% and 38.1% respectively.

Univariate analysis of tumor recurrence in UTUC patients

The patients were divided into the Recurrent Group (RG) and the Non-Recurrent Group (NRG) according to the follow-up outcomes. Univariate analysis was used to identify indicators with significant differences between the two groups. Results showed that hydronephrosis ($P=0.002$), T stage ($P=0.047$), NAC ($P<0.001$), chemotherapy cycle ($P=0.002$) and LVI ($P<0.001$) was associated with recurrence (Table 1) (Figure 1).

Multivariate Cox regression analysis for UTUC recurrence

The multivariate Cox regression analysis showed that

Table 1: Univariate analysis of the UTUC recurrence predictors.

Variables	Recurrent group (n=40)	Non-recurrent group (n=61)	χ^2	P
Gender				
Male	22 (55.0%)	33 (54.1%)	1.962	0.127
Female	18 (54.0%)	28 (45.9%)		
Age (years)				
<65	13 (32.5%)	22 (36.1%)	2.132	0.14
≥ 65	27 (67.5%)	39 (63.9%)		
Hydronephrosis				
Negative	31 (77.5%)	29 (47.5%)	9.798	0.002
Positive	9 (22.5%)	32 (52.5%)		
Tumor location				
Renal pelvis	14 (35.0%)	15 (24.6%)	1.193	0.551
Ureter	21 (52.5%)	35 (57.4%)		
Multifocal lesion	5 (12.5%)	11 (18.0%)		
Tumor side				
Left	18 (45.0%)	28 (45.9%)	0.301	0.583
Right	22 (55.0%)	33 (54.1%)		
T stage				
T1	3 (7.5%)	11 (18.0%)	7.948	0.047
T2	10 (25.0%)	21 (34.4%)		
T3	22 (55.0%)	25 (41.0%)		
T4	5 (12.5%)	4 (6.6%)		
LND				
Yes	35 (87.5%)	51 (83.6%)	2.635	0.105
No	5 (12.5%)	10 (16.4%)		
NAC				
Negative	38 (95.0%)	44 (72.1%)	14.566	<0.001
Positive	2 (5.0%)	17 (27.9%)		
Chemotherapy cycle				
12-Jan	24 (60.0%)	18 (29.5%)	9.477	0.002
03-Apr	16 (40.0%)	43 (70.5%)		
LVI				
Negative	16 (40.0%)	8 (13.1%)	20.131	<0.001
Positive	24 (60.0%)	53 (86.9%)		

UTUC: Upper Tract Urothelial Carcinoma; NAC: Neoadjuvant Chemotherapy; LVI: Lymphovascular Invasion; LND: Lymph Node Dissections

hydronephrosis (HR=2.622, 95% CI: 1.055-6.518, P=0.038), T stage (HR=1.662, 95% CI: 1.095-2.524, P=0.017) and LVI (HR=1.990, 95% CI: 1.003-3.947, P=0.049) were independent risk factors for UTUC recurrence; NAC (HR=0.209, 95% CI: 0.048-0.918, P=0.038) and chemotherapy cycle (HR=0.509, 95% CI: 0.264-0.981, P=0.044) were independent protective factors (Table 2).

Construction and validation of the nomogram model

We established a nomogram for better prediction of recurrence in UTUC patients based on the variables identified as significant factors in the multivariate Cox regression analysis (Figure 2). The C-index of internal validation was 0.791 (95% CI: 0.720-0.862), which indicated the good discrimination accuracy of the nomogram. The AUCROC of the nomogram to predict 1, 3 and 5-years RFS were 0.853 (95% CI: 0.751-0.955), 0.893 (95% CI: 0.810-0.975) and 0.903 (95% CI: 0.800-1.006) respectively (Figure 3). The calibration plot for the RFS probability at 1, 3 and 5-years revealed an optimal agreement between nomogram prediction and actual observation (Figure 4).

Discussion

This research retrospectively evaluated data from 101 UTUC patients who underwent RNU combined with GC intravenous chemotherapy to establish the relationship between relevant risk factors and survival outcomes. A direct correlation between hydronephrosis, T stage, NAC, chemotherapy cycle, LVI and lower RFS probability in UTUC patients after RNU combined with intravenous chemotherapy was observed.

The recurrence rate of UTUC after RNU is high, especially IVR, which accounts for 22% to 47%. Meanwhile, 2% to 6% of UTUC patients have a recurrence in the contralateral upper urinary tract [5]. The pathophysiological mechanism is unclear and may be

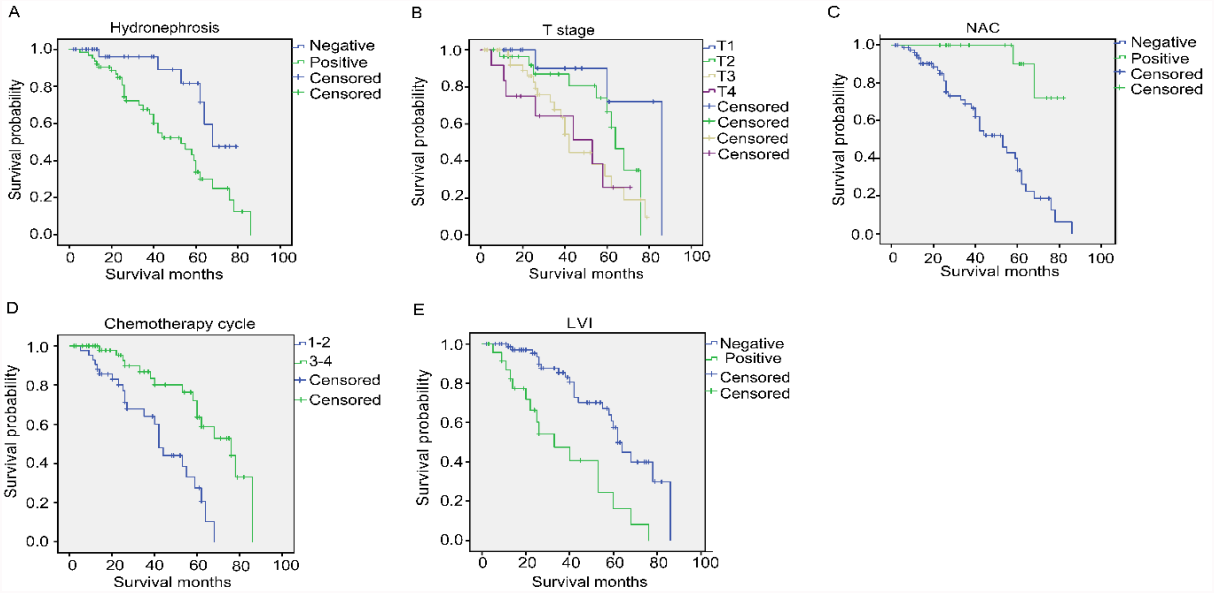

Figure 1: Kaplan–Meier plots of RFS according to the five significant variables: (A) Hydronephrosis; (B) T stage; (C) NAC; (D) Chemotherapy cycle; (E) LVI. RFS: Reelapse-Free Survival; NAC: Neoadjuvant Chemotherapy; LVI: Lymphovascular Invasion

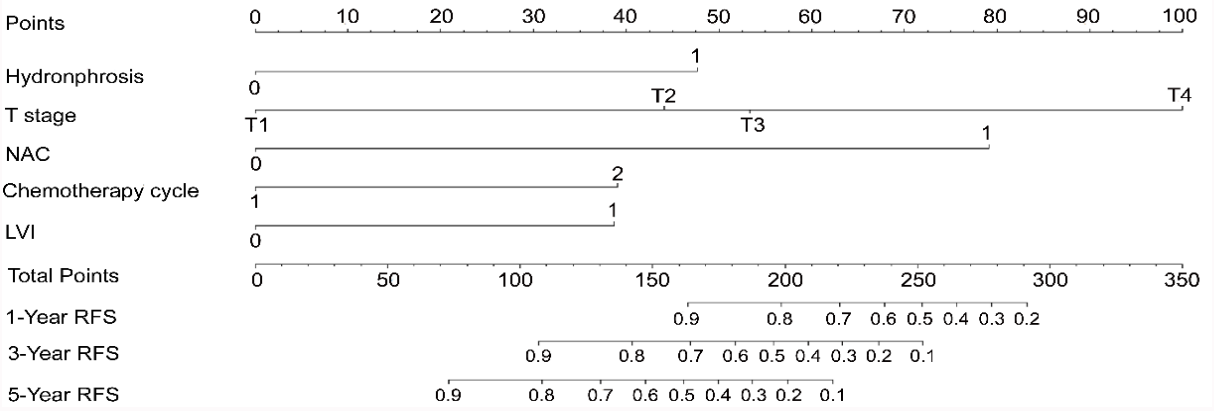

Figure 2: Nomogram for predicting RFSat 1-, 3- and 5-year in UTUC patients after RNU combined with chemotherapy. Hydronephrosis: 0 = negative, 1 = positive; NAC: Neoadjuvant Chemotherapy: 0 = negative, 1 = positive; Chemotherapy cycle: 1=3-4 cycles, 2=1-2 cycles; LVI: 0 = negative, 1 = positive; lymphovascular invasion: 0 = negative, 1 = positive; RFS: Relapse-Free Survival; UTUC: Upper Tract Urothelial Carcinoma; RNU: Radical Nephroureterectomy

Table 2: Multivariate Cox regression analysis of the predictor variables for UTUC recurrence.

	β	SE	Wald	df	Sig.	Exp (β)	95% CI for Exp (β)	
							Lower	Upper
Hydronphrosis	0.964	0.465	4.303	1	0.038	2.622	1.055	6.518
T stage	0.508	0.213	5.685	1	0.017	1.662	1.095	2.524
NAC	-1.566	0.755	4.301	1	0.038	0.209	0.048	0.918
Chemotherapy cycle	-0.675	0.335	4.068	1	0.044	0.509	0.264	0.981
LVI	0.688	0.349	3.877	1	0.049	1.99	1.003	3.947

UTUC: Upper Tract Urothelial Carcinoma; NAC: Neoadjuvant Chemotherapy; LVI: Lymphovascular Invasion

related to tumor implantation, tumor migration and cancerization of urinary tract epithelium. Currently, there are two hypotheses to explain the high UTUC recurrence rate at bladder after RNU with bladder cuff resection. The first is the field cancerization hypothesis: exposure of the entire urothelial epithelium to carcinogens can lead to multifocal and multiclonal carcinoma [9]. Another is the monoclonality hypothesis: The multiple carcinogens derived from monoclonal malignant cell spread throughout the entire urothelial epithelium and spread downstream [10]. Although several researchers indicated that the risk factors of IVR after RNU included male, history of transurethral resection of the bladder, smoking history, tumor site, tumor multifocality, tumor stage, operative approach, diagnostic ureteroscopy, positive surgical margin, etc. [11]. There is still no consensus on this issue. Lee et al. [12] evaluated

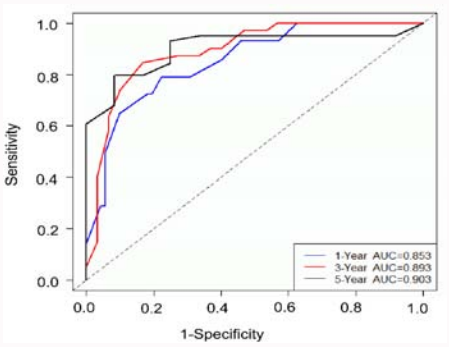

Figure 3: Receiver operating characteristic curve of the nomogram mode.

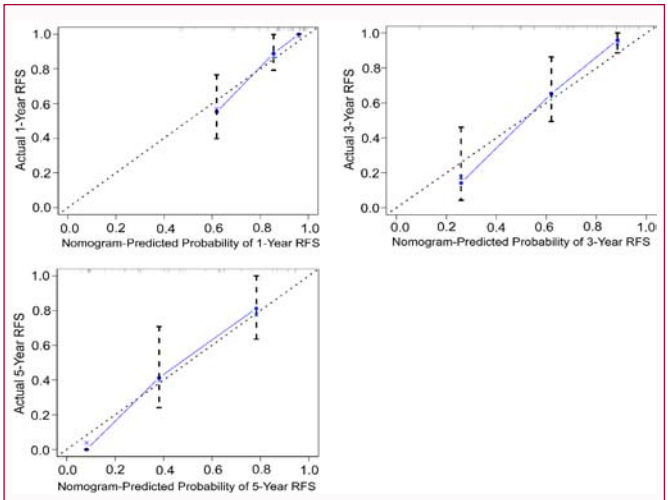

Figure 4: The calibration curve of the nomogram mode.
RFS: Relapse-Free Survival

the clinicopathological factors of IVR in 760 UTUC patients who underwent RNU. Among them, 231 (30.4%) experienced IVR. All patients were grouped according to whether IVR occurred. The results showed no significant difference between the 5-year CSS and OS of two groups. Multivariate analysis showed that hydronephrosis, tumor size, positive preoperative voided urine cytology and preoperative ureteroscopy before RNU were independent predictors of IVR. Predictors reducing the risk of IVR significantly included: Women, laparoscopic RNU, and treatment with AC. Another study showed that tumor multifocality was an important prognostic factor for IVR after RNU. In this study, 164 (29.8%) developed IVR and 30 (5.5%) developed contralateral upper urinary tract recurrence in 550 UTUC patients who underwent RNU surgery (median age: 68 years; median follow-up time: 40.3 months) [13]. It could be seen that the possibility of postoperative UTUC recurrence is still high. Although some studies showed that IVR did not affect the overall postoperative survival of UTUC patients [14], the recurrence of UTUC greatly increased their psychological and economic burden, thus lowering the quality of life for patients. At present, several domestic and foreign studies have found that perioperative chemotherapy could reduce the probability of tumor recurrence and improve the prognosis for UTUC patients. A 2020 multi-center Randomized Controlled Trial (RCT) study of 71 hospitals in the United Kingdom assessed the efficacy of systemic platinum-based chemotherapy on UTUC patients, with 132 patients receiving RNU combined with platinum-based AC and 129 receiving RNU alone. The results showed that GC chemotherapy within 90 days after RNU could significantly improve Disease-Free Survival (DFS) and Metastasis-Free Survival (MFS) in patients with locally advanced UTUC. The authors argued that platinum-based AC should be included as a new standard of care after RNU [15]. Therefore, it is important to identify the risk factors for tumor recurrence in UTUC patients to conduct scientific adjuvant therapy for some high-risk patients.

The ipsilateral hydronephrosis due to obstruction of the ureter is usually indicative of a larger or more aggressive UTUC. The appearance of hydronephrosis is not only related to the infiltration of UTUC, but also associated with the distant metastasis of UTUC and the death of patients. The hydronephrosis caused by UTUC usually indicates a higher stage of UTUC, most of which have reached T3 or even T4. This kind of hydronephrosis progresses rapidly and is more likely to damage renal function than hydronephrosis caused by other causes. It is difficult to remove by other interventions except for surgery and restricts the use of platinum-based chemotherapy, leading to a poor prognosis of the UTUC patients [16,17]. T stage has been proved to be the important factor affecting the RFS of UTUC patients. The higher the T stage, the higher the risk of UTUC metastasis and the worse the prognosis. The 5-year OS of pTa-pT1 patients is usually as high as 90%, while that of pT3 and pT4 patients is merely 30% to 50% and 10% to 20% respectively. The 5-year CSS of pT2/pT3 UTUC patients is less than 50%, while that of pT4 patients is less than 10% [2]. NAC is applied to eradicate micrometastasis, overcome the limitation of clinical staging and provide a survival benefit. Its advantage is that it could be delivered when patients still have adequate renal function prior to RNU. So, patients have better tolerance to chemotherapy and could be given higher chemotherapy dose. However, selection bias and overtreatment might limit the decision-making for the physicians due to the devoid of pathology results from the specimen of RNU. In addition, many patients who don't respond to NAC might have worse prognosis due to delayed surgery. A study by Makito et al. [18] demonstrated that NAC could down-grade ipsilateral hydronephrosis in UTUC patients. According to the results of Computed Tomography (CT) images, hydronephrosis was classified into five grades in this research. After NAC, 10 patients (31%), 21 patients (66%) and 1 patient (3%) experienced down-grading, no change and up-grading respectively. The research also showed that locally advanced tumor (cT3); pathological LVI and severe hydronephrosis (grade 3/4) were identified as prognostic factors for CSS and Progress-Free Survival (PFS) after NAC+RNU. It is also noteworthy that none of the patients with down-grading hydronephrosis died of UTUC during the follow-up. Fahad et al. [19] conducted a meta-analysis of 15378 UTUC patients in 22 studies, showing that NAC was associated with higher rate of pathological complete response and pathological down staging. NAC also could improve the OS and CSS in patients with locally advanced UTUC. The retrospective cohort study updated in 2019 found the UTUC patients who received NAC were more likely to degrade pathological staging than those receiving surgery alone. The overall odds ratio of NAC on down-staging was 0.21 (95% CI: 0.09-0.60, P=0.004) [20]. Urothelial malignant cells need blood vessels to provide nutrition during growth. And the abundant new vasculatures also provide a pathway for tumor cells to metastasize. LVI has been included in TNM staging system of lung cancer and many other tumors and proved to be an important prognostic factor for many malignant tumors, such as liver cancer, testicular cancer and penile cancer [21]. It could be used to predict tumor recurrence after RNU combined with chemotherapy, especially

in UTUC patients without lymph node metastasis or without lymph node dissection. A retrospective study showed that LVI was associated with advanced pathological tumor stage (P<0.001), tumor necrosis (P=0.012), lymph node metastasis (P=0.017) and tumor multifocality (P=0.012), with 28 (15.6%) identified LVI among 180 UTUC patients treated with RNU. Multivariate analysis indicated that LVI was an independent prognostic factor for RFS and CSS [22]. In a study of 139 stage II-IV UTUC patients who received RNU, the 5-year OS (67.1% *vs.* 33.7%; P=0.004), DFS (70.2% *vs.* 46.0%; P=0.030) and MFS (86.3% *vs.* 65.2%; P=0.048) of patients receiving AC were significantly better than those not receiving AC. However, there were no significant difference in the 5-year RFS between the two groups (78.2% *vs.* 62.5%; P=0.525). Importantly, the survival curves of high-stage UTUC patients who received AC were similar to low-stage UTUC patients who received RNU alone. Multivariate analysis showed that AC was an independent protective factor for OS (HR: 0.29, 95% CI: 0.129-0.654, P=0.003) [23].

This study had several limitations. First, this research was a single-center and retrospective study. A multicenter, prospective study with a larger sample size is needed to validate this nomogram model in the future. Second, the calibration plot for the survival outcomes probability revealed an optimal agreement at various time points in this cohort; however, we did not perform any external validation. The predictive accuracy of our nomogram in other cohorts should be further assessed.

Conclusion

As revealed by univariate and multivariate analysis, hydronephrosis, T stage, NAC, chemotherapy cycle and LVI were shown to be independent factors for OS and RFS in UTUC patients who underwent RNU combined with chemotherapy. The established nomogram could accurately predict the risk of recurrence in UTUC patients and had good clinical application value, which might be useful in UTUC patient risk stratification to help clinician's decision-making.

Ethics Approval and Consent to Participate

This study was approved by the Beijing Friendship Hospital, Capital Medical University Medical Science Research Ethics Committee (No. 2019-P2-011-01).

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