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ORIGINAL ARTICLE

Development and Validation of a Model for Predicting Intravesical Recurrence in Organ-confined Upper Urinary Tract Urothelial Carcinoma Patients after Radical Nephroureterectomy: a Retrospective Study in One Center with Long-term Follow-up

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Abstract
Although radical nephroureterectomy is the standard treatment method for upper urinary tract urothelial carcinoma, it is associated with a high risk of intravesical recurrence. There are no models for predicting IVR after RNU in patients with organ-confined UTUC. Therefore, we developed and validated a model for postoperative prediction of IVR after RNU. The development cohort consisted of 416 patients who underwent RNU with bladder cuff excision at our center between 1 January 2007 and 31 December 2015. Patient clinicopathologic data were recorded. Multivariate Cox proportional hazard ratio regression was used to build a predictive model with regression coefficients, backward step-wise selection was applied, and the likelihood ratio test with Akaike's information criterion was used as the stopping rule. An independent cohort consisting of 152 consecutive patients from 1 January 2016 and 31 December 2017 was used for validation. The performance of this predictive model was assessed with respect to discrimination, calibration, and clinical usefulness. The predictors in this model included tumor stage, tumor diameter, tumor location, and tumor grade. In the validation cohort, the model showed good discrimination, with a concordance index of 0.689 (95% CI, 0.629 to 0.748) and good calibration. Decision curve analysis demonstrated that the model was also clinically useful. This study presents a good model that may facilitate individualized postoperative prediction of IVR after RNU in patients with organ-confined UTUC, and thus, may help improve postoperative strategies and facilitate treatment outcomes.

Keywords Intravesical recurrence · Upper urinary tract urothelial carcinoma · Radical nephroureterectomy · Retrospective study

Introduction

Urothelial carcinomas (UCs) are the fourth most common tumors [1]. UC can be located in the upper or lower urinary tract. Upper urinary tract Urothelial carcinoma (UTUC) is uncommon, it accounts for only 5-10% of UC [2]. UTUCs are comprised of pyelocaliceal and ureteral tumors; the former is approximately twice as common as the latter. The estimated annual incidence of UTUCs is 2/100,000 persons, and this rate has risen in the past few years with improved medical detection technology [3]. However, the overall prognosis is poor: the 5-year specific survival is less than 50% for T2/T3 and less than 10% for T4 [4–6]. Asians seem to present with more advanced and higher grade tumors than other ethnicities [3].

Among patients with UTUC after radical nephroureterectomy (RNU), 30–50% have intravesical recurrence (IVR), mostly within the first year postoperatively [6]. Economic and health costs are increasing. Therefore, the detection of predictors of IVR in patients with UTUC after RNU is very important.

Individualized prediction of IVR in patients with UTUC after RNU could provide guidance in determining treatment programs and follow-up schedules. However, limited studies have addressed this issue and the conclusions were inconsistent. Although there are several predictive nomograms for detecting the risk factors of IVR [7], no research has focused on the prediction of IVR for patients with organ-confined UTUC after RNU. Therefore, the aim of this study was to develop a predictive model of IVR for Chinese patients with organ-confined UTUC after RNU.

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Methods

Patients

Ethical approval (Ethical Committee No. 2019PS029K) was provided by the Institutional Research and Ethics Committee of the Shengjing Hospital Affiliated China Medical University in Shenyang, China on 21 February 2019. Informed consent was obtained from all participant patients. The clinical research registry UIN is ChiCTR1900021626.

The development cohort of this study comprised 416 patients who underwent RNU with bladder cuff excision at our center between 1 January 2007 and 31 December 2015. The validation cohort comprised 152 consecutive patients from 1 January 2016 and 31 December 2017 who were selected through the same inclusion and exclusion criteria. Details about the cohort flow chart are shown in Supplement Fig. 1.

The inclusion criteria were as follows. The diagnosis of UTUC was confirmed by pathologic examination. All tumor stages were graded T1–T3 and had no adjacent organ invasion or lymph node metastasis. The exclusion criteria were as follows: patients who had distant metastasis (M1) or bilateral UTUC were excluded, and those who underwent neoadjuvant chemotherapy.

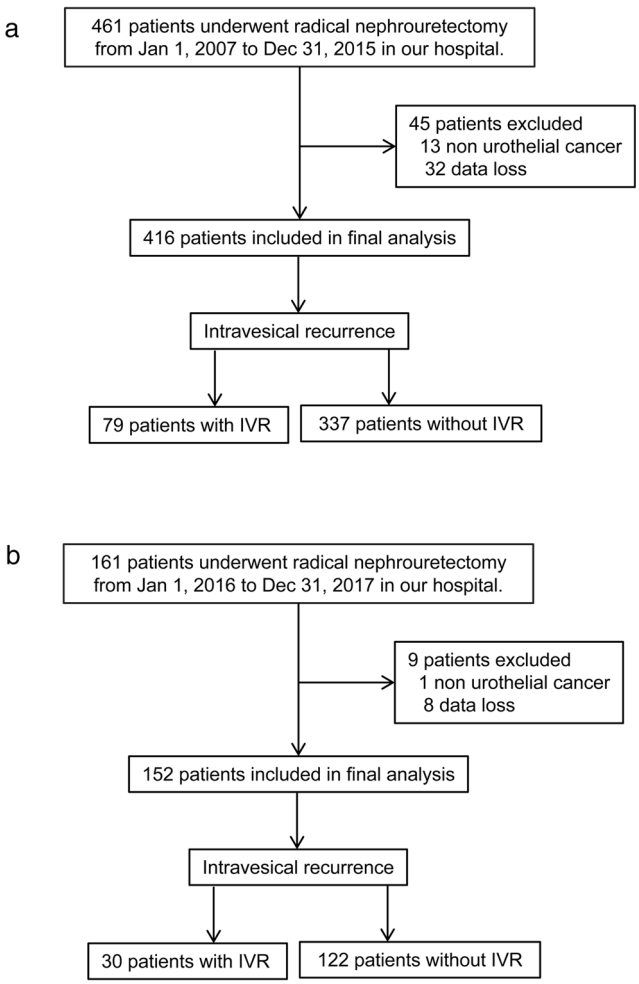

Fig. 1 Flow chart of the study. a Development cohort **b** Validation cohort. Abbreviation: IVR, intravesical recurrence

Baseline characteristics, outcomes and follow-up

Patient demographics (age, sex, and body mass index), comorbidity (diabetes mellitus, coronary heart disease, and hypertension), disease characteristics (tumor size, location, tumor grade, and tumor stage), history of smoking, history of transurethral resection of bladder tumors (TURB), surgical approach, and adjuvant chemotherapy data were recorded.

History of smoking was defined as a consecutive or cumulative smoking time longer than 6 months during the patient's lifetimes [8]. Tumor stage was according to International Union Against Cancer TNM classification. Tumor grade was according to 2004 World Health Organization (WHO) classification [9]. We divided tumor grade into three groups: low grade, high grade and high grade with squamous carcinoma (SC) or adenoid carcinoma (AC). Tumor location was classified as renal pelvic, ureteral upper middle part, ureteral lower part and multifocality. Ureteral lower part was defined as the part beyond the bifurcation of the iliac vessels [10]. Multifocality was defined as two or more pathologically confirmed tumors present synchronously in any location (renal pelvic or ureter). Tumor diameter was defined as either less than or equal to 2 cm or more than 2 cm [11], as measured by computed tomography. The surgical approach was defined as open surgery or laparoscopic surgery. The preoperative pathological method was classified as diagnostic ureteroscopy with biopsy, intraoperative frozen pathology, or non-preoperative pathology.

IVR was established only on the basis of pathologic evidence. IVR time was defined as the time from surgery to the time when the IVR was detected. Adjuvant chemotherapy comprised gemcitabine/cisplatin regimens [12]. Patients receive gemcitabine 1000 mg/m^2 on days 1, 8, and 15, then plus cisplatin 70 mg/m^2 on day 2. The cycles were repeated every 21 days [13]. Patients who received adjuvant chemotherapy were defined as those who had undergone this therapy at least once. All patients underwent adjuvant bladder instillation comprising a single dose of intravesical chemotherapy (pirarubicin) within 72 h after surgery. Thereafter, instillation was repeated every week for the first two months and then every month until 2 years. The follow up regimen was as follows: cystoscopy, urinary cytology, and computed tomography urography were performed every 3 months for the first 2 years, then every 6 months until 5 years, and annually thereafter.

Statistical analysis

Data were analyzed in SPSS 22.0 for Windows (IBM, Armonk, NY, USA), STATA 15.0. (Stata Corp., College Station, TX, USA) and R software (version 3.0.1; http://www.Rproject.org). The packages in R used in this study were 'rms' and 'glmnet.' The reported statistical significance levels were two-sided, and $p < 0.05$ was considered statistically significant.

The normality of continuous variables was determined with the Kolmogorov-Smirnov test. Normally distributed continuous variables are presented as the mean ± standard deviation. Non-normally continuous variables are presented as the median (interquartile range). Cox proportional hazard ratio regression was used for univariate analysis. Multivariate Cox proportional hazard ratio regression was used to build the predictive nomogram with regression coefficients. Backward step-wise selection was applied, and the likelihood ratio test with Akaike's information criterion was used as the stopping rule [14, 15].

The performance of this model was tested in an independent validation cohort. The Cox regression formula developed in the development cohort was applied to the validation cohort, and the probability for each patient at specific time points was calculated. To quantify the discrimination performance of this model, Harrell's concordance index (c-index) was measured, A c-index of 0.5 indicates no discrimination, whereas 1.0 indicates perfect discrimination. Calibration plots were used to assess the calibration of this model. Perfect calibration is depicted by a slope on the 45° line. Decision curve analysis was performed to determine the clinical utility of this model by quantifying the net benefits at different threshold probabilities in the validation cohort.

Results

Strictly according to the same inclusion and exclusion criteria, 416 patients were included in the development cohort, and 152 patients were included in the validation cohort. Seventy-nine patients (19.0%) in the development cohort had IVR after 49.00 months (40.00, 60.00) follow-up, whereas 30 patients (20%) in the validation cohort had IVR after 28.00 months (15.00, 35.75) follow-up.

According to univariate analysis of the development cohort, tumor stage, tumor diameter, tumor location, tumor grade, adjuvant chemotherapy, and tumor side were significantly associated with IVR (Table 1). Multivariate Cox proportional hazard ratio regression was used to build a predictive nomogram with regression coefficients. Backward step-wise selection ($p < 0.1$) was applied, and the likelihood ratio test with Akaike's information criterion was used as the stopping rule. The results are presented in the final model (tumor stage, tumor diameter, tumor location, and tumor grade). On the basis of these results, we developed a predictive model, from which a nomogram predicting IVR after RNU was generated (Table 2 and Fig. 2).

Each clinicopathologic feature corresponds to a specific point determined by drawing a line straight upward to the points axis. The sum of the points located on the total points axis represents the probability of cardiovascular morbidity, as determined by drawing straight down to the risk axis. For example, consider a patient with the following features: T2 stage (42 points); tumor diameter more than 2 cm (60 points); tumor location at the lower ureter (29 points), and high-grade urothelium carcinoma (96 points). The total number of points is 227, and the suspected probability of being IVR free at the 24th month is approximately 67%, whereas the suspected probability of being IVR free at the 48th month is approximately 59%. This calculated outcome can be used in decision-making for treatment plans.

The discrimination of this model was qualified by the concordance index. The concordance index was 0.689 (95% CI, 0.629 to 0.748) in the development cohort and 0.678 (95% CI,0.583 to 0.772) in the validation cohort. The calibration plots revealed good calibration in the validation cohort. In the decision curve analysis (details in Fig. 3a and b), the nomogram indicated a net benefit of the "treat all" strategy at the threshold probabilities ≥15% at 24 months and ≥ 18% at 48 months. Using the nomogram to predict IVR is beneficial (details in Fig. 3c and d).

Discussion

The overall prognosis of UTUC is poor, the tumor recurrence rate is high, and IVR is the most common recurrence site. Individualized and accurate prediction of IVR by physicians for patients with UTUC after RNU is very important to guide the development of treatment strategies and follow-up schedules. Previous studies addressing this issue have been limited, and models attempting to predict IVR are rare. Moreover, the conclusions have been controversial. Furthermore, data on Asians, who seem to present with more advanced and higher grade tumors, have not been reported to date. Therefore, we conducted this study to develop a model to predict IVR in Chinese patients with organ confined UTUC after RNU.

In our study, the rate of IVR after RNU was approximately 20%, which was lower than the rates reported in previous studies. The reason for this discrepancy may be that patients from our center all underwent intravesical chemical instillation after RNU [16–18]. This model ultimately retained four predictors with good discrimination, calibration and clinical net benefit: tumor stage, tumor location, tumor diameter, and tumor grade.

Table 1 Univariate analysis of patients in the development and validation cohorts

Number of patients	Development Cohort ($n = 416$)			Validation Cohort ($n = 152$)		
	Without IVR $n = 337$ (81%)	With IVR $n = 79$ (19%)	p value	Without IVR $n = 122$(80%)	With IVR $n = 30$ (20%)	p value
Follow up period (months)	38.00(22.00,54.50)	49.00(40.00,60.00)		24.50(10.00,35.25)	28.00(15.00,35.75)	
Demographic characteristics						
Mean age (years)	66.83 ± 10.03	65.24 ± 8.79	0.18	66.84 ± 9.69	67.83 ± 9.78	0.670
Sex (male/female)	168(49.85%)/169(50.15%)	45(56.96%)/34(43.04%)	0.21	63(51.64%)/59(48.36%)	18(60.00%)/12(40.00%)	0.448
BMI (kg/m^2)	23.92 ± 3.96	23.79 ± 4.31	0.535	23.64 ± 3.57	23.13 ± 4.22	0.396
Comorbidity						
Diabetes mellitus (yes)	38(11.28%)	6(7.59%)	0.254	9(7.38%)	2(6.67%)	0.744
The history of smoking (yes)	86(25.52%)	22(27.85%)	0.226	39(31.97%)	10(33.33%)	0.710
The history of TURB (yes)	8(2.37%)	2(2.53%)	0.742	1(0.82%)	1(3.33%)	0.301
Preoperative data						
Tumor side (left/right)	177(52.52%)/160(47.48%)	52(65.82%)/27(34.18%)	0.022	64(52.46%)/58(47.54%)	21(70.00%)/9(30.00%)	0.076
Tumor diameter (≤2 cm vs. > 2 cm)	116(34.42%)/221(65.58%)	12(15.19%)/67(84.81%)	0.006	43(35.25%)/79(64.75%)	5(16.67%)/25(83.33%)	0.099
Tumor location						
Renal pelvis	143(42.43%)	26(32.91%)	0.382	45(36.89%)	8(26.67%)	0.469
Upper or middle ureter	68 (20.18%)	18(22.78%)	0.159	30(24.59%)	6(20.00%)	0.544
Lower ureter	104 (30.86%)	27(34.18%)	0.526	42(34.43%)	14(46.67%)	0.657
Multifocality	22 (6.52%)	8(10.12%)	0.671	5(4.10%)	2(6.67%)	0.830
The method of obtaining pathology						
Without preoperative pathology	279(82.79%)	62(78.48%)	0.467	99(81.15%)	22(73.33%)	0.535
Intraoperative frozen biopsy	55(16.32%)	15(18.99%)	0.220	22(18.03%)	7(23.33%)	0.286
Ureteroscopy biopsy	3(0.90%)	2(2.53%)	0.280	1(0.82%)	1(3.33%)	0.398
Postoperative data						
Tumor stage						
Tis and T1	130(38.58%)	12(15.19%)	0.002	42(34.43%)	4(13.33%)	0.113
T2	158(46.88%)	48(60.76%)	0.001	64(52.46%)	19(63.33%)	0.041
T3	49(14.54%)	19(24.05%)	0.341	16(13.11%)	7(23.33%)	0.500
Tumor grade						
Low grade UC	67(19.88%)	2(2.53%)	0.020	18(14.75%)	1(3.33%)	0.410
High grade UC	248(73.59%)	69(87.34%)	0.008	96(78.69%)	26(86.67%)	0.189
High grade UC and SC or AC	22(6.53%)	8(10.13%)	0.725	8(6.56%)	3(10.00%)	0.681
Adjuvant chemotherapy	106(31.45%)	37(46.84%)	0.019	39(31.97%)	12(40.00%)	0.415

Continuous variables with normal distribution were reported as the mean ± standard deviation (SD), Continuous variables with non-normal distribution were reported as the median (interquartile range), categorical variables were reported as number (percentage). P value was obtained by univariate cox proportional hazard regression

BMI Body mass index, *TURB* Transurethral resection of bladder tumor, *UC* Urothelium carcinoma, *BT* Bladder tumor, *SC* Squamous carcinoma, *AC* Adenoid carcinoma

Tumor stage was closely related to the risk of IVR [19]. Terakawa et al. demonstrated that tumor stage was an independent risk factor for IVR, and higher tumor stage UTUC tended to have a higher IVR rate than lower tumor stage [20]. In line with these findings, in this study, we found that tumor stage was a predictor of IVR and that higher stage UTUC tended to have a higher IVR rate. This result may be due to the increasing potential of metastasis in higher stage UTUC. However, Hisataki et al. suggested that lower tumor stage was a significant risk factor for IVR [21]. The discrepancy may be because higher stage patients tend to receive adjuvant chemotherapy, which may decrease the rate of IVR. In our study, patients with high stage (T4) and positive lymph nodes were excluded; therefore, a smaller proportion of patients (34.3%) received adjuvant chemotherapy than that in the study by Hisataki et al. (43.5%).

According to EAU guidelines, the risk stratification of UTUC involves classification into low-risk and high-risk groups, in which tumor diameter was a significant factor [22]. Espiritu et al. [23] have also considered large tumor size to be a significant factor for poor recurrence outcomes. In our study, we considered larger tumor diameter (> 2 cm) to be a significant predictor of IVR in patients with organ-confined UTUC after RNU. The larger tumor diameter might increase the fragility of the tumors, thus leading to cancer cells floating to the bladder. However, Yang et al. [24] have reported that tumor size is not a

Table 2 Multivariate cox proportional hazard regression for IVR

Intercept and Variables	HR	95% CI	P
Tumor location	1.183	0.983,1.423	0.075
Tumor diameter	2.619	1.409,4.866	0.002
Tumor stage	1.636	1.165,2.298	0.004
Tumor grade	1.773	1.087,2.893	0.022
Concordance index			
Development Dataset	0.689	0.710, 0.823	
Validation Dataset	0.678	0.677, 0.857	

The odds ratio,and 95% confidence interval were measured through cox proportional hazard regression, backward step-wise selection ($p < 0.1$)

Abbreviations: OR, odds ratio; CI, confidence interval

significant factor in IVR. This finding may be a result of the different classification standards: the cutoff value in the study by Yang et al. was 3 cm, compared with 2 cm in our study.

Narukawa et al. reported that tumor grade is a risk factor for IVR [25]. Giovanni et al. [6] suggested tumor grade was strictly related to the tumor aggressiveness. In our study, the result suggested tumor grade was a significant predictor of IVR. IVR was regarded as field cancerization with implantation [26, 27]. Additionally, high grade tumor might have higher potential to intravesical implantation. However, Yang et al. [24] suggested tumor grade was not associated significantly with IVR which in line with the study of Elawdy et.al [28]. This lack of association might be a result of the higher proportion of low-grade UTUC patients in Yang's study (31.97%) compared with our study (16.59%).

Tumor location has been considered a risk factor for IVR, although this conclusion is controversial [17, 29]. Both Li WM et al. and Novara G et al. [18, 29] found that tumor location was a significant risk factor in IVR. In contrast, Yang et al. [24] have opposite results. Our results suggested that tumor location was a significant predictor of IVR. The closer the location to the bladder, the higher the risk of IVR. The anatomic proximity might increase the chance of cancer cells floating into bladder. Novara et al. [30] found that tumor multifocality has prognostic value in UTUC patients. Our study indicated that multifocality seemed to the associated with higher risk than the proximity to the bladder.

In a large sample meta-analysis, Seisen T et al. [19] have found that male sex was a significant risk factor, possibly because of the hormonal differences in tumor biology [31, 32] and female sex tends to be associated with a higher risk of urothelial carcinoma-specific mortality [33]. In our research, we found that sex was not a significant predictor, possibly because of the different ethnicity and the exclusion of T4 stage patients in our study.

Pignot G et al. [34] suggested that a previous history of bladder cancer was a significant factor in IVR. However, in contrast, Akdogan et al. [35] rejected this conclusion, which was the same as ours. This may have been influenced by the small proportion of patients having a history of TURB (4.90%) and all patients having regular intravesical chemical instillation after TURB in our center.

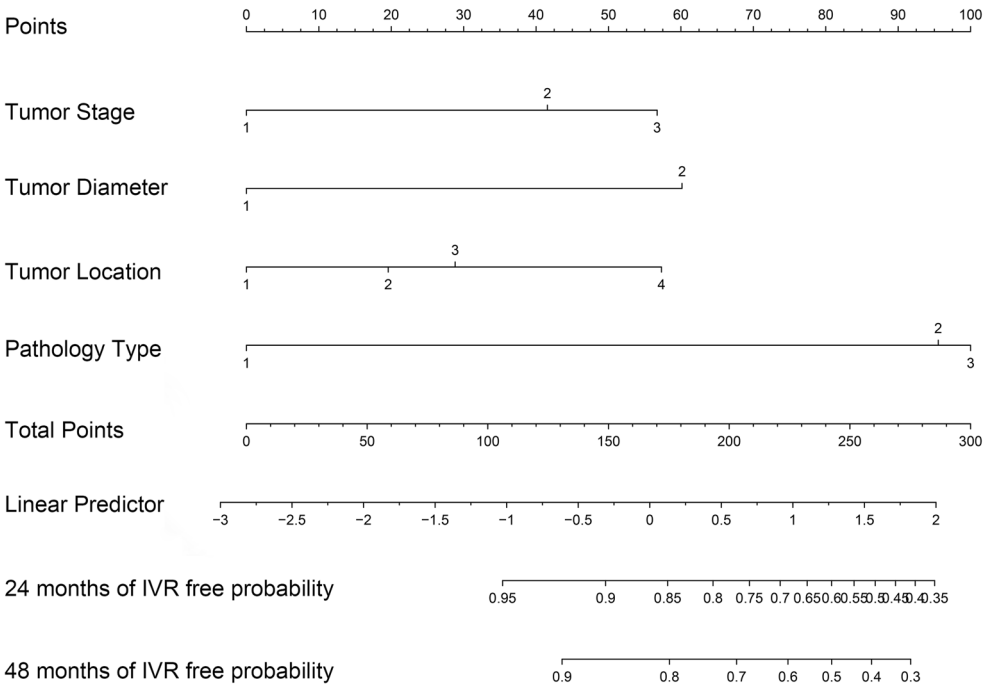

Fig. 2 Nomogram of IVR prediction in organ-confined UTUC patients after RNU. Tumor stage: 1, pT1; 2, pT2; 3, pT3; Tumor diameter: 1, tumor diameter < 2 cm; 2, tumor diameter ≥ 2 cm; Tumor location: 1, renal pelvic; 2, ureteral upper middle part; 3. ureteral lower part; 4, multifocality; Tumor grade: 1, Low grade UC; 2, High grade UC; 3, High grade UC and SC or AC. Abbreviations: IVR, intravesical recurrence; RNU, Radical nephroureterectomy; UC, urothelium carcinoma; SC, squamous carcinoma; AC, adenoid carcinoma; UTUC, upper urinary tract urothelium carcinoma

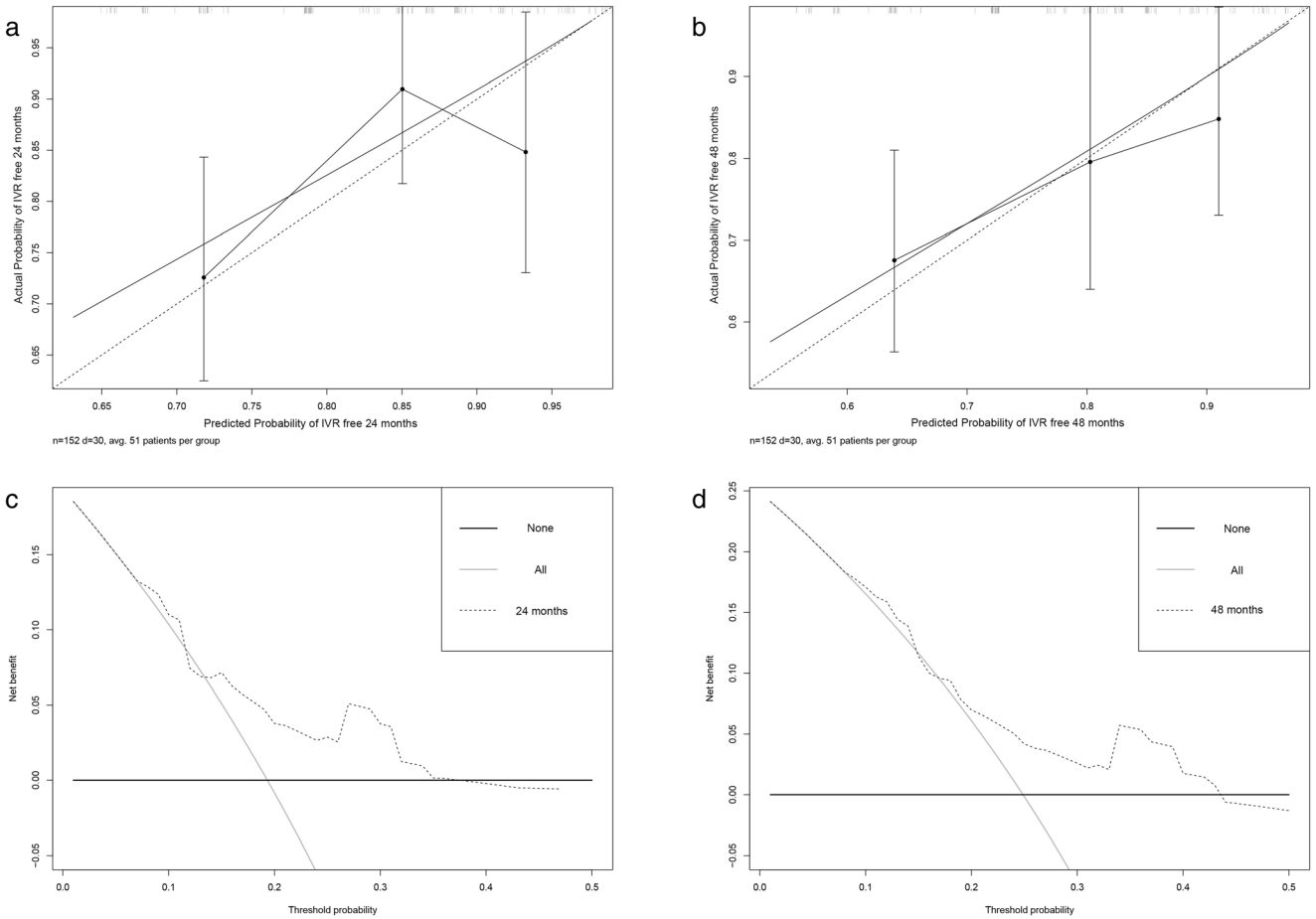

Fig. 3 Calibration and DCA in validation cohort. a Calibration at 24th month**. b** Calibration at 48th month. **c** DCA at 24th month. **d** DCA at 48th month. Abbreviation: DCA, Decision curve analysis

Sung et al. [36] suggested that preoperative ureteroscopy biopsy was associated with IVR, owing to field cancerization with implantation. However, this conclusion is inconsistent with our results, possibly because relatively few patients underwent preoperative ureteroscopy biopsy in our study (3.43%) compared with the previous study (44.7%).

Fradet et al. [37] suggested that history of smoking was not a risk factor in IVR. Our findings were consistent with this conclusion. However, Hagiwara et al. and Xylinas et al. [38, 39] found a significant correlation between history of smoking and IVR. This conclusion may have been influenced by different definitions of smoking status and the change in postoperative smoking status.

There were several limitations in this study. First, this was a retrospective study from one center. Second, some clinicopathologic variables were not collected in our study; thus, potentially introducing deviations, such as urine cytology. Third, some risk factors used to stratify patients, such as the cutoff value of tumor diameter was various, which could potentially reduce the accuracy of the results. To avoid these limitations, a multicenter prospective cohort with standard methods would be required to validate this model, especially in western centers. Nonetheless, this is the first model reported to predict IVR in Chinese patients with organ confined UTUC after RNU, and this nomogram can be used by physicians and patients easily.

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Author contributions Song Bai 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: Song Bai.

Acquisition of data, analysis and interpretation of data: Song Bai, Xuanyu Zhang .

Drafting of the manuscript and critical revision of the manuscript for important intellectual content: Xuanyu Zhang.

Statistical analysis: Xuanyu Zhang.

Obtaining funding and other (figures): Song Bai.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no competing interests.

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