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Preoperative predictive model and nomogram for disease recurrence following radical nephroureterectomy for high grade upper tract urothelial carcinoma

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Abstract

Purpose: To identify preoperative risk factors for disease recurrence, following radical nephroureterectomy (RNU) for upper tract urothelial carcinoma (UTUC), and to create a predictive nomogram.

Materials and methods: Based on a multicenter database, we identified patients who underwent RNU due to high grade UTUC. Urothelial carcinoma of the bladder or contralateral UTUC was not considered as recurrence. Cox regression model was used to determine the effect of different preoperative variables as predictors of recurrence.

Results: Two hundred and forty-five patients were included in the analysis. The 2 and 5 years recurrence rates were 16.3% and 19.2%, respectively. Factors associated with recurrence on univariable analysis were sessile architecture hazard ratio (HR) 3.16 (95% CI, 1.38–7.26, $P = 0.006$), ≥cT3 disease HR 2.30 (95% CI, 1.12–4.72, $P= 0.023$), age >65 HR 2.02 (95% CI, 1.00–4.05, $P= 0.048$), Eastern Cooperative Group > 0 HR 1.98 (95% CI, 1.09–3.57, $P= 0.023$), hydronephrosis HR 1.93 (95% CI, 1.04–3.57, $P= 0.035$). Higher hemoglobin levels HR 0.81 (95% CI, 0.69–0.96, $P= 0.013$) and preoperative estimated glomerular filtration rate ≥ 50 HR 0.48 (95% CI, 0.25–0.92, $P = 0.028$) were associated with lower probability for recurrence. Multivariable analysis identified sessile architecture as the only independent predictor of recurrence HR 2.52 (95% CI, 1.09–5.86, $P= 0.0308$). C-index of 0.71 was calculated for a predictive model including all variables in the multivariable analysis, indicating good predictive accuracy. A nomogram predicting 2 and 5 year recurrence free probability was developed accordingly.

Conclusions: Based on a multicenter database, we developed a nomogram with good predictive accuracy for recurrence following RNU. This may serve as an aid in decision-making regarding the use of neoadjuvant chemotherapy.

Keywords: Upper tract urothelial carcinoma; UTUC; Recurrence; Nomogram; Metastasis; Nephroureterectomy

1. Introduction

Upper tract urothelial carcinoma (UTUC) is a relatively uncommon genitourinary cancer accounting for 5% to 10%

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of urothelial malignancies [1,2]. Unlike urothelial carcinoma of the bladder (UCB), most UTUC tumors are invasive at the time of diagnosis [3,4], leading to relatively high recurrence rates of >30% at 5 years [5].

High level evidence suggest a significant survival benefit associated with neoadjuvant, cisplatin-based chemotherapy (NAC), for the treatment of muscle invasive UCB [6,7]. Successful integration has been predicated in part on accurate preoperative staging through transurethral resection of bladder tumors. Recently, adjuvant chemotherapy after radical nephroureterectomy (RNU) has demonstrated a survival benefit in a randomized controlled trial [8]. Nevertheless, many patients experience significant decline in kidney function following RNU and are no longer eligible for cisplatin-based chemotherapy following surgery [9–12].The use and evidence for NAC for UTUC is less robust and therefore utilization in clinical practice is more limited. Decision-making regarding the use of NAC is particularly challenging in UTUC due to difficulties with accurate staging as a consequence of small biopsy samples and limitations of current imaging. Hence, proper patient selection for neoadjuvant chemotherapy, balancing the potential benefits vs. the risk of overtreatment is of utmost importance.

In this study we sought to determine predictors of disease recurrence following RNU based on preoperatively available data. We develop a nomogram predicting individualized risk of recurrence, which may aid in proper patient selection for neoadjuvant chemotherapy.

2. Materials and methods

2.1. Study design and patient eligibility

This study is a retrospective analysis of a multicenter UTUC database including all patients who underwent RNU due to UTUC in 3 referral centers in the United States between 1993 and 2016. Institutional review board approval was obtained locally by each participating center as needed and deidentified data was used for the combined database analysis. Requirement for informed consent was waived by the IRB.

The database was queried for patients who had an initial diagnosis of nonmetastatic high grade (HG) UTUC based on either biopsy or positive cytology. Patients who received neoadjuvant chemotherapy or underwent prior cystectomy due to UCB were excluded (Fig. 1). Patients generally had follow-up at the participating institutions, including evaluation at 3 and 6 months after RNU and every 6 to 12 months thereafter. Follow-up generally included a history, physical examination, routine blood work, cystoscopy, urine cytology, and imaging.

2.2. End point definition

Recurrence was defined as any visceral, local, or nodal disease documented following RNU. UCB or contralateral UTUC were not considered as recurrence for the purpose of this study.

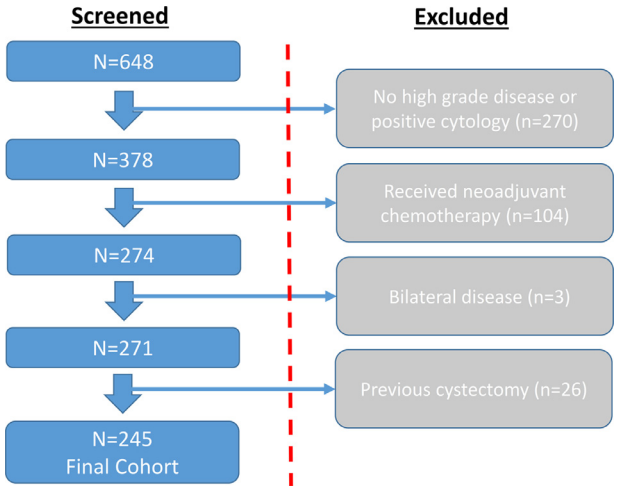

Fig. 1. Patient selection flowchart.

2.3. Statistical analysis

Covariates assessed as possible predictors of recurrence were age, gender, race, body mass index, symptoms, Eastern Cooperative Group (ECOG) performance status, American Society of Anesthesiologists score, history of bladder cancer, hydronephrosis, tumor size, tumor architecture (papillary vs. sessile – subjectively assigned by the surgeon in case of intraluminal findings), tumor focality, tumor location, locally advanced disease on imaging (cT3) preoperative estimated glomerular filtration rate (eGFR), hemoglobin levels and performance of lymph node dissection.

Summary statistics for patient characteristics were reported using mean and standard deviation for continuous variables, and using counts and percentages for categorical variables. Patient tumor, and imaging characteristics were compared between patients with recurrence and patients without recurrence using 2-sample t test for continuous variables and using the chi-square test for categorical variables. The recurrence-free survival was estimated using the Kaplan-Meier method. Univariable and multivariable Cox regression analyses were used to assess the association between recurrence-free survival and patient, tumor, and imaging characteristics. Variables with a univariable Pvalue of 0.1 or less were entered in a multivariable regression model, and multiple imputation chained equations [13] were used to impute missing data. Hazard ratios (HR) and 95% confidence intervals (CI) were reported. Two-sided Pvalues were reported and a Pvalue less than 0.05 was considered statistically significant. The bootstrap validation method was used to estimate the bias-corrected or overfitting-corrected predictive accuracy of the model, which is presented by concordance index (C-index). A nomogram was developed to predict the 2-year and 5-year recurrence-free probabilities for the

multivariable regression model with the highest C-index. All analyses were conducted using SAS version 9.4 (SAS Institute Inc. Cary, NC).

3. Results

3.1. Cohort characteristics

A total of 245 patients with nonmetastatic UTUC who underwent RNU were included in the final cohort. Cohort characteristics are described in Table 1. After a median follow-up of 27 months, disease recurrence was identified in 20% (49/245) of patients. The 2- and 5-year recurrence rates were 16.3% (40/245) and 19.2% (47/245) respectively. Patients who had disease recurrence had lower mean hemoglobin levels, higher proportion of sessile tumors and of tumors located in the renal pelvis (Table 1).

3.2. Prediction of recurrence

Variables evaluated as predictors of recurrence are described in Table 2 and include: sessile architecture HR 3.16 (95% CI, 1.38−7.26), cT3 disease HR 2.30 (95% CI, 1.12−4.72), age >65 HR 2.02 (95% CI, 1.00−4.05), ECOG>0 HR 1.98 (95% CI, 1.09−3.57), hydronephrosis HR 1.93 (95% CI, 1.04−3.57), hemoglobin level HR 0.81 (95% CI, 0.69−0.96) and preoperative eGFR ≥ 50 HR 0.48 (95% CI, 0.25−0.92). Multivariable logistic regression model (Table 2) identified sessile architecture as the only

Table 1
Cohort characteristics.

		Total ($n = 245$)		No recurrence ($n = 196$)		Had recurrence ($n = 49$)		P value
		n	%	n	%	n	%	
Age, years (Mean ± SD)		70 ± 9.8		70 ± 10.0		71 ± 9.0		0.5454
Gender	Female	93	38.0%	77	39.3%	16	32.7%	0.4160
	Male	152	62.0%	119	60.7%	33	67.3%	
Race	White	205	90.3%	164	90.6%	41	89.1%	0.8365
	Black	9	4.0%	7	3.9%	2	4.3%	
	Other	13	5.7%	10	5.5%	3	6.5%	
BMI, kg/m^2 (Mean ± SD)		29.0 ± 6.4		29.2 ± 6.5		28.1 ± 5.6		0.2708
ECOG performance status	0	126	56.3%	106	59.2%	20	44.4%	0.0927
	≥1	98	43.7%	73	40.8%	25	55.6%	
ASA Score	≤2	70	31.8%	57	32.4%	13	29.5%	0.6267
	3	138	62.7%	108	61.4%	30	68.2%	
	4	12	5.5%	11	6.3%	1	2.3%	
HgB, g/dl (mean ± SD)		12.9 ± 1.8		13.0 ± 1.7		12.4 ± 1.7		**0.0438**
eGFR, ml/min/m^2 (mean ± SD)		61.7 ± 21.4		62.3 ± 21.6		59.1 ± 20.9		0.3253
History of bladder cancer	No	162	66.9%	129	66.5%	33	68.7%	0.8645
	Yes	80	33.1%	65	33.5%	15	31.3%	
symptoms	No	72	29.4%	56	28.6%	16	32.7%	0.6009
	Yes	173	70.6%	140	71.4%	33	67.3%	
Hydronephrosis	None/mild	162	69.5%	136	71.6%	26	60.5%	0.1983
	Moderate/severe	71	30.5%	54	28.4%	17	39.5%	
Tumor location (imaging)	Renal pelvis	116	52.7%	89	49.7%	27	65.9%	**0.0293**
	Ureter	85	38.6%	71	39.7%	14	34.1%	
	Both	19	8.6%	19	10.6%	0	0.0%	
Tumor focality (imaging)	Unifocal	179	83.6%	146	83.9%	33	82.5%	0.8147
	Multifocal	35	16.4%	28	16.1%	7	17.5%	
Tumor size, cm (mean ± SD)		3.36 ± 2.28		3.40 ± 2.24		3.21 ± 2.46		0.4990
Clinical T stage[a]	<T3	179	84.8%	150	87.2%	29	74.4%	0.0509
	≥T3	32	15.2%	22	12.8%	10	25.6%	
Tumor location (Ureteroscopy)	Renal	114	50.4%	88	48.4%	26	59.1%	0.4360
	Ureter	94	41.6%	78	42.9%	16	36.4%	
	Both	18	8.0%	16	8.8%	2	4.5%	
Tumor focality (Ureteroscopy)	Unifocal	143	84.6%	122	83.6%	21	91.3%	0.5349
	Multifocal	26	15.4%	24	16.4%	2	8.7%	
Architecture	Papillary	185	91.1%	156	93.4%	29	80.6%	**0.0224**
	Sessile	18	8.9%	11	6.6%	7	19.4%	
Lymph node dissection	No	112	47.3%	88	46.3%	24	51.1%	0.6255
	Yes	125	52.7%	102	53.7%	23	48.9%	

ASA = American Society of Anesthesiologists; BMI = basal metabolic index; ECOG = Eastern Cooperative Oncology Group; eGFR = Estimated glomerular filtration rate; HgB = Hemoglobin; SD = standard deviation.

[a] Based on presurgical imaging.

Table 2
Univariable and multivariable analysis.

		Univariable		Multivariable	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, years	<66	Reference		Reference	
	≥66	2.020 (1.006−4.056)	**0.048**	1.856 (0.825−4.175)	0.1349
Gender	Male	Reference			
	Female	0.747 (0.411−1.357)	0.337		
Race	White	Reference			
	Non-white	1.362 (0.538−3.448)	0.514		
BMI (continuous)		0.969 (0.919 - 1.021)	0.239		
Symptoms	Yes	Reference			
	No	1.182 (0.651−2.148)	0.582		
ECOG	0	Reference		Reference	
	≥1	1.981 (1.098−3.573)	**0.023**	1.468 (0.786−2.739)	0.2279
ASA	2	Reference			
	3	1.351 (0.700−2.607)	0.370		
	4	0.704 (0.091−5.435)	0.736		
History of Bladder Cancer	No	Reference			
	Yes	1.004 (0.545−1.850)	0.989		
HgB (continuous)		0.814 (0.691−0.958)	**0.013**	0.912 (0.761−1.094)	0.3200
eGFR	<50	Reference			
	≥50	0.489 (0.258−0.928)	**0.028**	0.673 (0.340−1.332)	0.2554
Hydronephrosis	No	Reference		Reference	
	Yes	1.931 (1.045−3.571)	**0.035**	1.816 (0.977−3.377)	0.0594
Tumor location (imaging)	Kidney	Reference			
	Ureter	0.762 (0.400−1.454)	0.409		
Tumor focality (imaging)	Unifocal	Reference			
	Multifocal	1.145 (0.506−2.590)	0.745		
Tumor size (continuous)		0.977 (0.832−1.146)	0.771		
Clinical T stage[a]	<T3	Reference		Reference	
	≥T3	2.299 (1.119−4.725)	**0.023**	1.722 (0.839−3.533)	0.1381
Tumor location (ureteroscopy)	Kidney	Reference			
	Ureter	0.841 (0.451−1.569)	0.586		
	Both	0.558 (0.132 - 2.354)	0.427		
Tumor focality (ureteroscopy)	Unifocal	Reference			
	Multifocal	0.573 (0.134−2.448)	0.452		
Architecture	Papillary	Reference		Reference	
	Sessile	3.167 (1.381−7.260)	**0.006**	2.527 (1.090−5.861)	**0.0308**
Lymph node dissection	No	Reference			
	Yes	0.947 (0.534−1.679)	0.852		

HR = hazard ratio; CI = confidence interval; BMI = basal metabolic index; ECOG = Eastern Cooperative Oncology Group; ASA = American Society of Anesthesiologists; HgB = hemoglobin; eGFR = estimated glomerular filtration rate.
[a] Based on presurgical imaging.

independent predictor of recurrence, HR 2.52 (95% CI, 1.09−5.86). Kaplan-Meier curves were plotted (Fig. 2) stratifying patients based on the number of risk factors (HB dichotomized at 12.4 g/dl). Patients with ≤3 risk factors had a 5-year recurrence free survival of 78%, compared to those with >3 risk factors who had a recurrence free survival of 43% (log rank test, $P < 0.0001$).

3.3. Nomogram development and validation

Based on the variables described above, a nomogram was developed for predicting disease recurrence following RNU (Fig. 3). C-index was calculated to evaluate the predictive value of the model. The bootstrap corrected C-index was 0.71 indicating good predictive ability. Calibration plots of the nomogram are provided in supplementary Fig. 1.

4. Discussion

Neoadjuvant, cisplatin-based chemotherapy (NAC) for the treatment of UCB is based on level 1 evidence and has an established role in the treatment algorithms of the disease [14]. Recent high level data suggest that adjuvant chemotherapy has an important role in UTUC [8], yet, after RNU many patients may be ineligible for such treatment due to decline in renal function [9−11]. NAC for UTUTC was associated with improved disease-specific survival and overall survival, yet the evidence supporting this is mainly

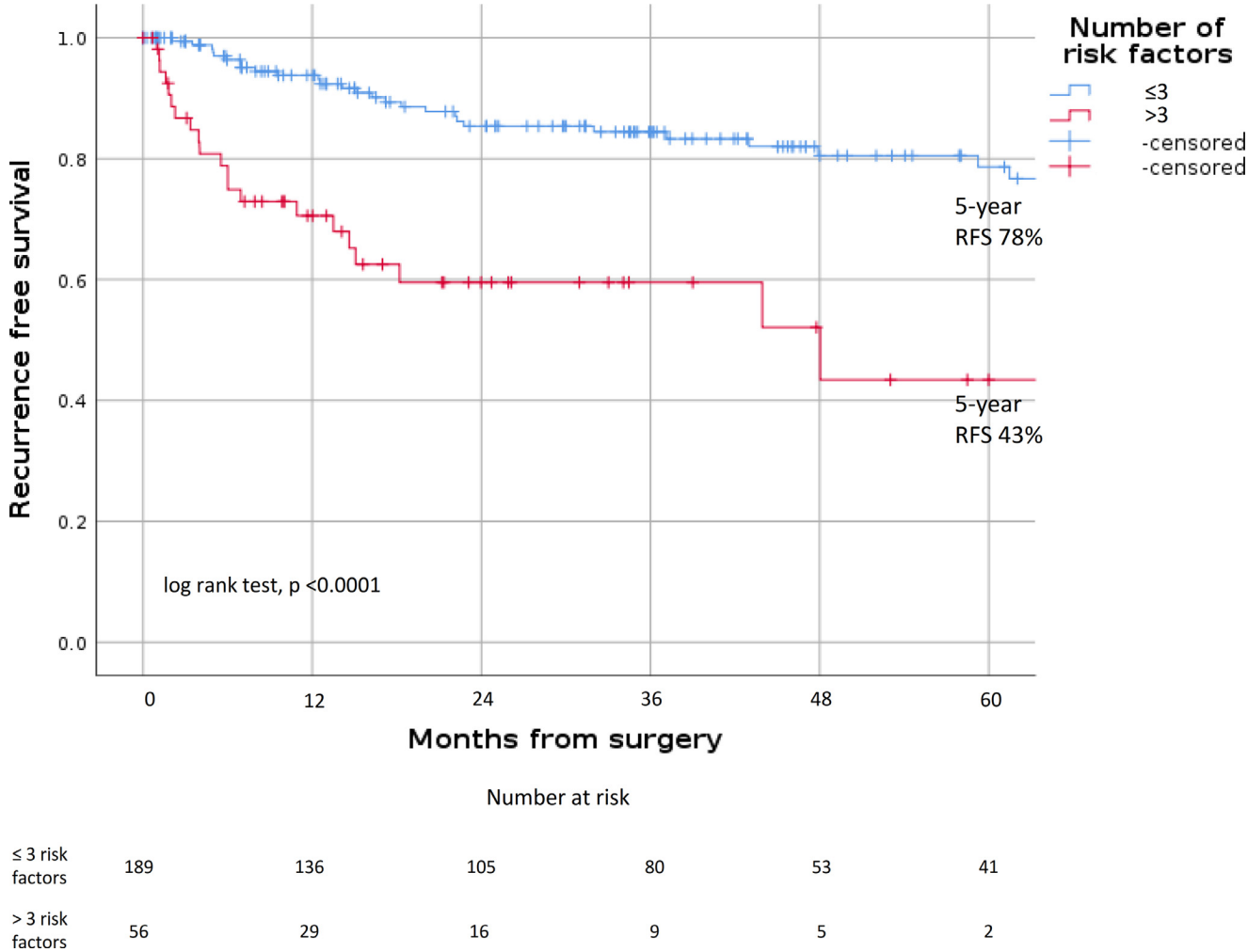

Fig. 2. Kaplan-Meier curves for recurrence free survival stratified based on number of risk factors.

based on small studies or retrospective cohorts [12]. Despite the potential benefit, data suggest that NAC for UTUC is extremely underutilized [15]. For those ineligible for cisplatin-based adjuvant chemotherapy, alternative regimens show decreased efficacy [12], making proper patient selection for NAC imperative.

In this study we developed a nomogram for individualized prediction of the risk of disease recurrence following RNU for HG UTUC. Older age (>65 years), ECOG score >0, the presence of hydronephrosis and ≥cT3 disease, sessile architecture, low eGFR (<50) and lower hemoglobin levels were all associated with recurrence. Several of these factors have been previously identified as associated with adverse pathological outcomes. Brien et al. found that hydronephrosis, positive cytology and HG biopsy results were associated with muscle invasive disease or non−organ-confined disease at RNU [16]. Favaretto et al. reported on HG biopsy results and signs of local invasion on imaging as predictors of muscle invasive or non−organ-confined disease [17]. Margulis et al. found that HG disease and sessile architecture were associated with non−organ-confined disease, recurrence and worse cancer-specific survival [18]. Similar to those reports, our analysis suggest that imaging related parameters such as hydronephrosis and cT3 disease were associated with recurrence. Interestingly, the only independent predictor of recurrence was sessile appearance of the tumor during initial diagnostic ureteroscopy. Both Margulis et al. and Krabbe et al. similarly found this factor to be associated with recurrence after RNU. Petros et al. have recently shown sessile tumors to be associated with non−organ-confined disease at the time of RNU [19]. This is further supported by evidence suggesting that sessile tumor architecture in RNU specimens is associated with more aggressive disease [20,21]. This information is readily available and is appreciated by the urologic surgeon as part of the initial standard evaluation of UTUC patients. Although in some cases there is limited evidence of intraluminal disease, we believe that when sessile tumors are found, even in the absence of additional risk factors, this should raise specific concerns and NAC should be considered. Since patients with low-risk disease are not candidates for neoadjuvant chemotherapy, only patients with HG

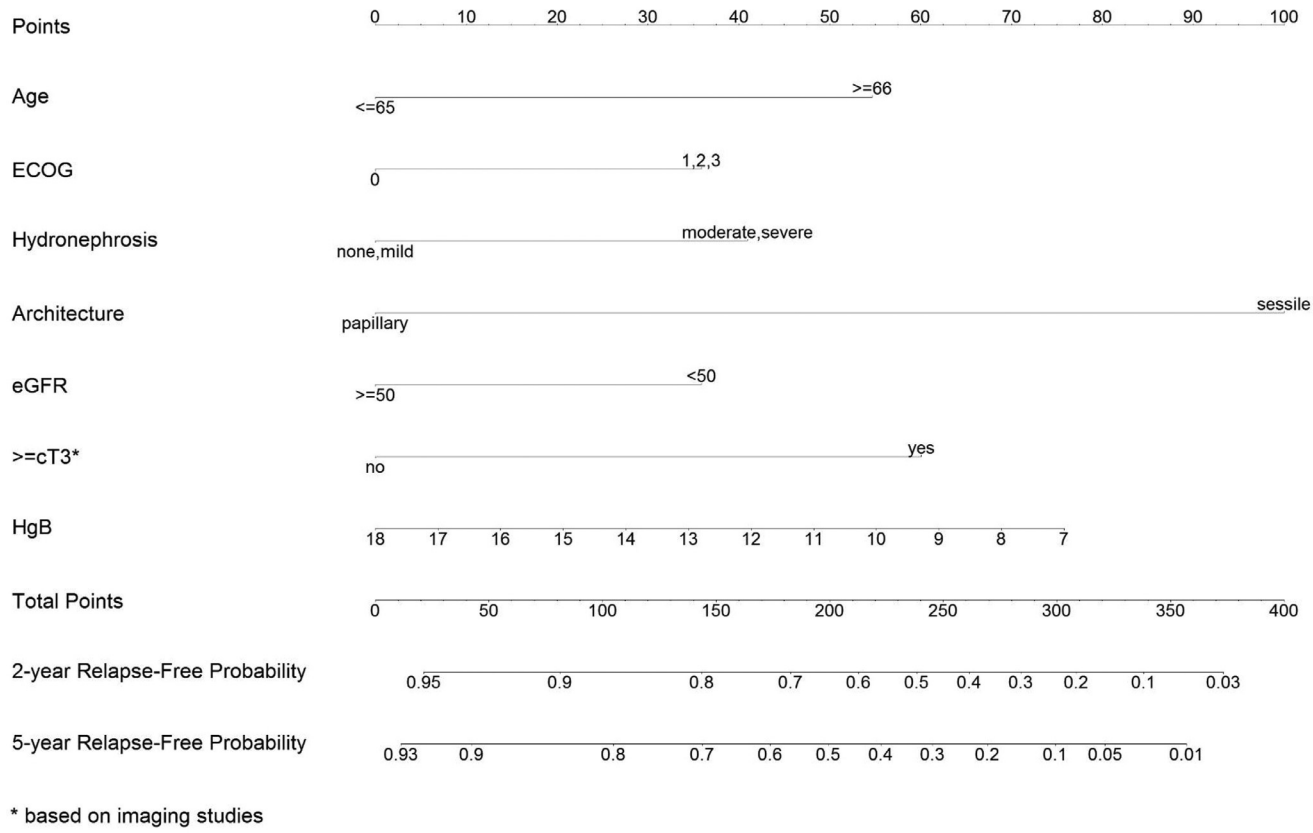

Fig. 3. Nomogram for prediction of 2 and 5 years recurrence rates following radical nephroureterectomy.

disease proven by either biopsy or positive cytology were initially included in our analysis. As such, biopsy grade and cytology were not considered in our predictive model.

Older age, higher ECOG score and decreased eGFR were also associated with increased risk of recurrence in our model. While some of these factors may not necessarily indicate more aggressive disease they may influence physicians' tendency for the use of adjuvant systemic therapy. Undertreatment is a known problem in elderly population and was shown to affect survival in elderly patients with UCB [22]. Based on our nomogram, a 70-year-old patient with ECOG 1 and no other risk factor will automatically accumulate 90 points which correspond to almost 20% risk of recurrence at 5 years. These results indicate that older patients with impaired performance status and renal function, may very well be at higher risk of recurrence following RNU and should not be automatically excluded from consideration of neoadjuvant chemotherapy.

Most of the currently available predictive models [16–19,23] are focused on predicting invasive or non–organ-confined disease at RNU, or, predicting recurrence / survival after surgery, using data which is not available prior to surgery, such as final pathology [5,24,25]. Adverse pathology on RNU specimen is an important end point and is associated with adverse outcomes [18,26]; however, since not all patients with invasive disease will develop recurrence, we believe that a preoperative predictive model for disease recurrence following surgery, may serve as a more useful aid for decision-making regarding the use of NAC. We suggest using this nomogram to further evaluate patients eligible for NAC before surgery, for those with low-risk NAC may be differed, thus lowering the rates of overtreatment and the associated side effects. Further considerations may rely on predictive models evaluating postoperative renal function and eligibility for adjuvant treatment [27]. In another scenario, those at high risk, especially with impaired renal function at baseline, should be strongly encouraged to receive NAC. Our model is based on multicenter database, and integrates perioperative clinical data obtained by the various modalities used for staging and diagnosis of UTUC, including ureteroscopy, imaging, and laboratory studies. The nomogram demonstrates an accuracy of 71% after internal validation, indicating a good predictive model. Based on the simplicity of use and the data needed, which is readily available in daily practice, we hope this may prove to be a useful tool for the treating physician.

Several limitations of our study should be noted. First this is a retrospective analysis and should be reviewed as such. Second this model is based on data from 3 referral centers with no external validation, which may impact the applicability of this model to the general patient population. Third, as mentioned above, since data regarding adjuvant therapies is not available prior to surgery this was not

included in the analysis, yet this may obviously influence recurrence rates.

5. Conclusions

We developed a nomogram for individualized risk calculation of disease recurrence following RNU due to HG UTUC. The nomogram is based on readily available clinical information and demonstrates good predictive accuracy of 71%. This nomogram may be used as a tool for preoperative risk assessment and guide decision-making on the use of neoadjuvant chemotherapy. External validation of this nomogram is needed.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.06.009.

References

[1] Rouprêt M, Babjuk M, Compérat E, et al. European association of urology guidelines on upper urinary tract urothelial Carcinoma: 2017 update. Eur Urol 2018;73:111–22.
[2] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA: A Cancer J Clin 2018;68:7–30.
[3] Freifeld Y, Krabbe L-M, Clinton TN, et al. Therapeutic strategies for upper tract urothelial carcinoma. Expert Rev Anticancer Ther 2018;8:1–10.
[4] Margulis V, Shariat SF, Matin SF, et al. Outcomes of radical nephroureterectomy: a series from the upper tract urothelial carcinoma collaboration. Cancer 2009;115(6):1224–33.
[5] Krabbe L-M, Eminaga O, Shariat SF, et al. Postoperative nomogram for relapse-free survival in patients with high grade upper tract urothelial carcinoma. J Urol 2017;197(3, Part 1):580–9.
[6] Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003;349(9):859–66.
[7] Vale CL. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data: advanced bladder cancer (ABC) Meta-analysis collaboration. Eur Urol 2005;48(2):202–6.
[8] Birtle AJ, Chester JD, Jones RJ, et al. Results of POUT: A phase III randomised trial of perioperative chemotherapy versus surveillance in upper tract urothelial cancer (UTUC). J Clin Oncol 2018;36(6_suppl):407-.
[9] Kaag MG, O'Malley RL, O'Malley P, et al. Changes in renal function following nephroureterectomy may affect the use of perioperative chemotherapy. Eur Urol 2010;58(4):581–7.
[10] Lane BR, Smith AK, Larson BT, et al. Chronic kidney disease after nephroureterectomy for upper tract urothelial carcinoma and implications for the administration of perioperative chemotherapy. Cancer 2010;116(12):2967–73.
[11] Xylinas E, Rink M, Margulis V, et al. Impact of renal function on eligibility for chemotherapy and survival in patients who have undergone radical nephro-ureterectomy. BJU Int 2013;112(4):453–61.
[12] Leow JJ, Martin-Doyle W, Fay AP, et al. A systematic review and meta-analysis of adjuvant and neoadjuvant chemotherapy for upper tract urothelial carcinoma. Eur Urol 2014;66(3):529–41.
[13] White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. Stat Med 2010;30(4):377–99.
[14] Alfred Witjes J, Lebret T, Compérat EM, et al. Updated 2016 EAU guidelines on muscle-invasive and metastatic bladder cancer. Eur Urol 2017;71(3):462–75.
[15] Cohen A, Kuchta K, Park S. Neoadjuvant and adjuvant chemotherapy use in upper tract urothelial carcinoma. Urologic Oncol Semin Orig Invest 2017;35(6):322–7.
[16] Brien JC, Shariat SF, Herman MP, et al. Preoperative hydronephrosis, ureteroscopic biopsy grade and urinary cytology can improve prediction of advanced upper tract urothelial carcinoma. J Urol 2010;184:69–73.
[17] Favaretto RL, Shariat SF, Savage C, et al. Combining imaging and ureteroscopy variables in a preoperative multivariable model for prediction of muscle-invasive and non-organ confined disease in patients with upper tract urothelial carcinoma. BJU Int 2012;109:77–82.
[18] Margulis V, Youssef RF, Karakiewicz PI, et al. Preoperative multivariable prognostic model for prediction of nonorgan confined urothelial carcinoma of the upper urinary tract. J Urol 2010;184:453–8.
[19] Petros FG, Qiao W, Singla N, et al. Preoperative multiplex nomogram for prediction of high-risk nonorgan-confined upper-tract urothelial carcinoma. Urol Oncol Semin Orig Invest 2019;37(4):292.e1–9.
[20] Remzi M, Haitel A, Margulis V, et al. Tumour architecture is an independent predictor of outcomes after nephroureterectomy: a multi-institutional analysis of 1363 patients. BJU Int 2009;103(3):307–11.
[21] Fritsche H-M, Novara G, Burger M, et al. Macroscopic sessile tumor architecture is a pathologic feature of biologically aggressive upper tract urothelial carcinoma. Urol Oncol Semin Orig Invest 2012;30(5):666–72.
[22] Guancial EA, Roussel B, Bergsma DP, et al. Bladder cancer in the elderly patient: challenges and solutions. Clin Interv Aging 2015;10:939–49.
[23] Singla N, Fang D, Su X, et al. Preoperative predictors of nonorgan-confined disease in upper-tract urothelial carcinoma differ between china and the united states. Urol Oncol 2018;36(3):88.e11–18.
[24] Isbarn H, Jeldres C, Shariat SF, et al. Location of the primary tumor is not an independent predictor of cancer specific mortality in patients with upper urinary tract urothelial carcinoma. J Urol 2009;182(5):2177–81.
[25] Jeldres C, Sun M, Lughezzani G, et al. Highly predictive survival nomogram after upper urinary tract urothelial carcinoma. Cancer 2010;116(16):3774–84.
[26] Lughezzani G, Burger M, Margulis V, et al. Prognostic factors in upper urinary tract urothelial carcinomas: a comprehensive review of the current literature. Eur Urol 2012;62:100–14.
[27] Sorbellini M, Kattan Michael W, Snyder Mark E, et al. Prognostic nomogram for renal insufficiency after radical or partial nephrectomy. J Urol 2006;176(2):472–6.