Original Paper

Urologia Internationalis

Urol Int 2016;96:57–64
DOI: 10.1159/000433606

Received: April 23, 2015
Accepted: May 27, 2015
Published online: July 1, 2015

Prediction of Locally Advanced Urothelial Carcinoma of the Bladder Using Clinical Parameters before Radical Cystectomy – A Prospective Multicenter Study

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Key Words
Bladder cancer · Radical cystectomy · Nomogram · Outcome

Abstract
Introduction: We aimed at developing and validating a pre-cystectomy nomogram for the prediction of locally advanced urothelial carcinoma of the bladder (UCB) using clinicopathological parameters. ***Materials and Methods:*** Multicenter data from 337 patients who underwent radical cystectomy (RC) for UCB were prospectively collected and eligible for final analysis. Univariate and multivariate logistic regression models were applied to identify significant predictors of locally advanced tumor stage (pT3/4 and/or pN+) at RC. Internal validation was performed by bootstrapping. The decision curve analysis (DCA) was done to evaluate the clinical value. ***Results:*** The distribution of tumor stages pT3/4, pN+ and pT3/4 and/

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0042–1138/15/0961–0057$39.50/0

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or pN+ at RC was 44.2, 27.6 and 50.4%, respectively. Age (odds ratio (OR) 0.980; p < 0.001), advanced clinical tumor stage (cT3 vs. cTa, cTis, cT1; OR 3.367; p < 0.001), presence of hydronephrosis (OR 1.844; p = 0.043) and advanced tumor stage T3 and/or N+ at CT imaging (OR 4.378; p < 0.001) were independent predictors for pT3/4 and/or pN+ tumor stage. The predictive accuracy of our nomogram for pT3/4 and/or pN+ at RC was 77.5%. DCA for predicting pT3/4 and/or pN+ at RC showed a clinical net benefit across all probability thresholds. ***Conclusion:*** We developed a nomogram for the prediction of locally advanced tumor stage pT3/4 and/or pN+ before RC using established clinicopathological parameters.

Introduction

Locally advanced tumor stages, including pathologic tumor stages pT3/4 and/or lymph node involvement (pN+) of urothelial carcinoma of the bladder (UCB) in patients undergoing radical cystectomy (RC) are associated with high treatment failure rates and reduced disease-specific survival [1]. Clinical tumor stage based on transurethral resection of the bladder (TUR-BT) shows a considerable discrepancy when compared with the final pathologic stage obtained from the RC specimen. It has been demonstrated that almost 50% of patients treated with RC for clinical T1G3 UCB were upstaged to muscle-invasive disease (MIBC) with 33.4% having non-organ-confined disease [2]. A reliable prediction of locally advanced stages of UCB may help improve risk stratification and thus optimize the selection of candidates for multimodal treatment. The quality of treatment may be increased by better patient counseling on neoadjuvant chemotherapy (NAC), intraoperative strategies, for example, extended lymphadenectomy, as well as nerve-sparing techniques and choice of urinary diversion.

Nomograms have been developed to predict locally advanced UCB or the likelihood of upstaging at the time of RC [3, 4]. An external validation of 2 nomograms demonstrated that the ability to predict pT3/4 stages or lymph node metastasis is limited and not necessarily conferrable to other cohorts [3, 5].

In order to optimize the accuracy of existing prediction tools, a statistical adjustment for relevant preoperative parameters is important. Taking into account multiple clinical variables in the preoperative setting, we developed and validated a pre-cystectomy nomogram using preoperative variables in order to predict locally advanced UCB.

Materials and Methods

Study Population

This study was approved by an institutional review board with all participating sites providing the necessary data-sharing agreement within the 'PROspective MulticEnTer RadIcal Cystectomy Series 2011' (PROMETRICS 2011). A total of 18 European centers (15 German, 2 Austrian, and 1 Italian) prospectively collected data resulting in a database comprising 679 consecutive patients undergoing RC for muscle-invasive or high-risk bladder cancer between January 1, 2011 and December 31, 2011. A total of 342 patients (50.3%) were excluded due to missing information on lymphovascular invasion (LVI) (n = 177) and muscularis propria (n = 119) at the time of last TUR-BT or evidence of distant metastases (n = 46). In total, 337 patients were eligible for the final analysis in the current investigation.

Data Assessment

Preoperative baseline patient characteristics were assessed and documented at admission for RC and included continuous variables such as age, gender and the number of TUR-BT. Categorical variables that were recorded at time of TUR-BT before RC were American Society of Anaesthesiologists Score (ASA, coded ASA1/2 vs. ASA3/4), tumor stage (coded ≥cT3 vs. cT2 vs. cTa, cTis, cT1), concomitant carcinoma in situ (CIS, coded presence vs. absence), tumor grading (coded G2/3 vs. G1), LVI (coded presence vs. absence) and tumor stage depending on the presence of muscularis propria in the specimen (coded ≥cT2 vs. cTa, cTis, cT1 without muscularis propria and ≥cT2 vs. cTa, cTis, cT1 with presence of non-tumor-infiltrated muscularis propria). In addition, tumor stage (coded ≥T3 vs. <T3) and/or nodal stage (coded N+ vs. N–) at the computed tomography (CT), hydronephrosis (coded presence vs. absence) before RC and NAC (coded administered vs. not administered) were assessed as well. NAC was recorded only when patients received at least one complete cycle of chemotherapy. Histopathological stages were classified according to the 2009 TNM classification [6]. Histopathological evaluation was conducted by experienced uropathologists at each center according to standard protocols. Radiological evaluation in terms of clinical tumor and nodal stage was assessed by pre-RC imaging (CT) performed by experienced radiologists. The objective of our study was to evaluate the impact of clinicopathological features obtained from the last TUR-BT and preoperative staging imaging before RC on the prediction of a locally advanced tumor stage pT3/4 and/or pN+.

Statistical Analysis

Medians and interquartile ranges (IQR) were generated for continuously coded variables; frequencies and proportions were generated for categorical variables. The Mann-Whitney and Chi-square test were used to assess differences in medians and proportions, respectively. Univariate and multivariate logistic regression models were calculated to evaluate the impact of age, gender, ASA-score, number of TUR-BTs before RC, tumor stage, CIS, tumor grading, LVI, tumor stage depending on the presence of muscularis propria in the specimen at the last TUR-BT before RC, tumor and nodal stage at CT, preoperative hydronephrosis and the administration of NAC on the prediction of a locally advanced tumor stage pT3/4 and/or pN+ at RC. Backward elimination relied on Akaike's information criterion to identify the most informative predictors of a locally advanced tumor stage after RC [7]. Based on

the logistic regression coefficients, a nomogram to individually predict the risk of pT3/4 and/or pN+ tumor stage was developed. A calibration plot graphically explored the correlation between model predicted and observed regarding pT3/4 and/or pN+ at RC. The internal validity of the models was evaluated by bootstrapping. In 1,000 bootstrap samples, the coefficients of the final regression model were estimated and tested in the original sample. The difference between the coefficients in the original sample and bootstrap samples as reflected by the slope index is the measure for the amount of 'optimism'. Normally, slope values are located between 0 and 1. A slope value of 1 means no optimism. PA of each model was quantified using the area under the receiver operating characteristics curve [8].

The decision curve analysis (DCA) was carried out to evaluate the clinical value of the prediction of pT3/4 and/or pN+ of our newly developed model vs. none, all and clinical tumor stage ≥2 at the last TUR-BT before RC [9, 10]. Analyses were conducted using the R statistical package (v.2.12.2) and the Statistical Package for Social Science 20.0 (SPSS Inc., Chicago, Ill., USA). All tests were two-sided with the statistical significance level set at $p \leq 0.05$.

Results

Descriptive Characteristics

A total of 50.4% (n = 170) displayed a locally advanced tumor stage pT3/4 and/or pN+ at RC. The distribution of tumor stages pT3/4, pN+ and pT3/4 and/or pN+ at RC was 44.2, 27.6 and 50.4%, respectively. Table 1 gives a detailed illustration of the descriptive characteristics. The number of TUR-BTs before RC ($p = 0.032$), higher clinical tumor stage ($p < 0.001$), presence of concomitant CIS ($p = 0.037$), presence of LVI ($p = 0.011$), higher clinical tumor stage in dependence of the muscularis propria ($p < 0.001$), tumor stage <T3, nodal stage N– at CT ($p < 0.001$) and hydronephrosis before RC ($p < 0.001$) were significantly associated with a locally advanced tumor stage pT3/4 and/or pN+, respectively (table 1).

Prediction of pT3/4 and/or pN+

Clinical tumor stage ≥cT3 vs. cTa, cTis, cT1 (odds ratio (OR) 4.342; $p < 0.001$) and clinical tumor stage cT2 vs. cTa, cTis, cT1 (OR 3.889; $p = 0.030$), concomitant CIS (OR 0.564; $p = 0.031$), LVI (OR 2.224; $p = 0.010$), clinical tumor stage in dependence of muscularis propria ≥cT2 vs. cTa, cTis, cT1 with presence of tumor-free muscularis propria (OR 3.292; $p < 0.001$), hydronephrosis (OR 2.644; $p < 0.001$), tumor stage ≥T3 and/or N+ at CT (OR 5.053; $p < 0.001$), respectively, were significantly associated with pT3/4 and/or pN+ at RC in univariate logistic regression analysis (table 2a).

In multivariate logistic regression analysis addressing the prediction of pT3/4 and/or pN+, age (OR 0.980; $p < 0.001$), clinical tumor stage ≥cT3 vs. cTa, cTis, cT1 (OR 3.367; $p < 0.001$), clinical tumor stage cT2 vs. cTa, cTis, cT1 (OR 3.476; $p = 0.058$), hydronephrosis (OR 1.844; $p = 0.043$), and tumor stage ≥T3 and/or N+ at CT (OR 4.378; $p < 0.001$), respectively, were the final variables of the model calculated in backward elimination (table 2b). The slopes of this model after 1,000 bootstrap samples within the internal validation were between 0.76 and 0.89. The inherent nomogram of our newly developed model can be seen in figure 1a showing a predictive accuracy (PA) of 77.5% in our study population.

In addition, the DCA showed that the application of our nomogram predicting pT3/4 and/or pN+ at RC was associated with a higher net benefit over all thresholds compared to a clinical tumor stage ≥cT2 (fig. 1b).

Compared to a reduced model (cT-stage of TUR-BT and radiological assessment), our nomogram always shows a net benefit above the 42% threshold (fig. 1c).

Discussion

Locally advanced UCB (stage pT3/4 and/or pN+) is associated with reduced long-term survival following RC [1, 11]. Staging before RC is often inaccurate and the discrepancy between staging based on TUR-BT and final tumor stage of the cystectomy specimen represents a significant problem [2, 12–14]. Among potential reasons for this phenomenon are varying quality of TUR-BT, low sensitivity of preoperative staging and increasing time intervals between TUR-BT and RC [1, 3]. An exact staging and prediction of advanced UCB is an essential requirement for adequate clinical decision making. We developed a pre-cystectomy nomogram including age, clinical tumor stage ≥cT3, presence of hydronephrosis before RC and tumor stage ≥T3 or N+ at CT imaging in order to predict pT3/4 and/or pN+ at RC. The PA of our nomogram was 77.5% and showed a net benefit by DCA.

A pre-cystectomy nomogram for the prediction of advanced UCB stage has previously been developed by Karakiewicz et al. [3]. Multivariate models for the prediction of tumor stages pT3/4 and pN+ showed an accuracy of 75.7 and 63.1%, respectively. The nomograms were more accurate than the tumor stage at TUR-BT alone [3]. May et al. [5] externally validated both nomograms implemented by Karakiewicz based on data of 2,477 patients of a German cohort treated by RC. They found a relatively low PA of 67.5 and 54.5% for the prediction of tumor stage pT3/4 and pN+, respectively [5]. The predic-

Table 1. Descriptive characteristics

Variables	Entire population (n = 337) (100%)	pT3/4 and/or pN+		p value
		yes (n = 170) (50.4%)	no (n = 167) (49.6%)	
Age at RC, years, median (IQR)	69 (62–76)	69 (62–76)	69 (62–76)	0.979
Gender				0.668
Male	278 (82.5)	142 (83.5)	136 (81.4)	
Female	59 (17.5)	28 (16.5)	31 (18.6)	
ASA-score				0.547
1	20 (5.9)	8 (4.7)	12 (7.2)	
2	164 (48.7)	79 (46.5)	85 (50.9)	
3	146 (43.3)	79 (46.5)	67 (40.1)	
4	7 (2.1)	4 (2.4)	3 (1.8)	
Number of TUR-BTs before RC, mean ± SD	1.80±1.36	1.71±1.32	1.88±1.40	0.032
Clinical tumor stage				<0.001
cTa	18 (5.3)	3 (1.8)	15 (9.0)	
cTis	11 (3.3)	2 (1.2)	9 (5.4)	
cT1	73 (21.7)	22 (12.9)	51 (30.5)	
cT2	223 (66.2)	136 (80.0)	87 (52.1)	
cT3	3 (0.9)	1 (0.6)	2 (1.2)	
cT4	9 (2.7)	6 (3.5)	3 (1.8)	
Concomitant CI S at last TUR-BT before RC				
Present	76 (22.6)	30 (17.6)	46 (27.5)	0.037
Absent	261 (77.4)	140 (82.4)	121 (72.5)	
Grading at last TUR-BT before RC				0.758
G1/G2	49 (14.5)	26 (15.3)	23 (13.8)	
G3	288 (85.5)	144 (84.7)	144 (86.2)	
LVI at last TUR-BT before RC				
Present	54 (16.0)	36 (21.2)	18 (10.8)	0.011
Absent	283 (84)	134 (78.8)	149 (89.2)	
Clinical tumor stage in dependence of muscularis propria				<0.001
cTa, cTis, cT1 without muscularis propria	53 (15.7)	17 (10.0)	36 (21.6)	
cTa, cTis, cT1 with presence of tumor-free muscularis propria	49 (14.5)	10 (5.9)	39 (23.4)	
≥cT2	235 (69.7)	143 (84.1)	92 (55.1)	
Tumor stage at CT before RC				
<T3	255 (75.7)	109 (64.1)	146 (87.4)	<0.001
≥T3	82 (24.3)	61 (35.9)	21 (12.6)	
Nodal stage at CT before RC				
N–	279 (82.8)	123 (72.4)	156 (93.4)	<0.001
N+	58 (17.2)	47 (27.6)	11 (6.6)	
Tumor and nodal stage at CT before RC				<0.001
<T3 and N–	229 (68.0)	29 (40.3)	200 (75.5)	
≥T3 and N+	108 (32.0)	43 (59.7)	65 (24.5)	
Hydronephrosis before RC				
Present	79 (23.4)	54 (31.8)	25 (15.0)	<0.001
Absent	258 (76.6)	116 (68.2)	142 (85.0)	
NAC				0.722
Administered	7 (2.1)	3 (1.8)	4 (2.4)	
Not administered	330 (97.9)	167 (98.2)	163 (97.6)	

Figures in parentheses are percentages.
SD = Standard deviation; c = clinical tumor stage in TUR-BT specimen.

Table 2. Prediction of pT3/4 and/or pN+ at RC

a Univariate logistic regression model addressing prediction of pT3/4 and/or pN+ at RC

Variables	Prediction of pT3/4 and/or pN+ at RC			
	OR	95% confidence interval		p value
		lower	upper	
Age at RC (cont.)	1.002	0.981	1.024	0.846
Female gender (ref.: male)	0.865	0.493	1.518	0.614
Number of TUR-BTs before RC (cont.)	0.911	0.776	1.071	0.258
Clinical tumor stage				
≥cT3 vs. cTa, cTis, cT1	4.342	2.593	7.272	<0.001
≥cT2 vs. cTa, cTis, cT1	3.889	1.138	13.292	0.030
Tumor grading G2/G3 at last TUR-BT before RC (ref.: G1)	0.885	0.482	1.623	0.692
Presence of concomitant CIS at last TUR-BT before RC (ref.: absence)	0.564	0.335	0.948	0.031
Presence of LVI at last TUR-BT before RC (ref.: absence)	2.224	1.206	4.101	0.010
Clinical tumor stage in dependence of muscularis propria				
≥cT2 vs. cTa, cTis, cT1 without muscularis propria	0.543	0.220	1.339	0.185
≥cT2 vs. cTa, cTis, cT1 with presence of tumor-free muscularis propria	3.292	1.747	6.202	<0.001
Presence of hydronephrosis before RC (ref.: absence)	2.644	1.550	4.509	<0.001
ASA-score 3/4 at RC (ref.: ASA-score 1/2)	1.322	0.860	2.032	0.203
No administration of NAC (ref.: administration)	0.732	0.161	3.322	0.686
Tumor stage ≥T3 and/or N+ at CT before RC (ref.: <T3 and pN–)	5.053	3.019	8.460	<0.001

b Final step of the backward eliminated multivariate regression model addressing the prediction of pT3/4 and/or pN+ at RC

Variables	Prediction of tumor stage pT3/4 and/or nodal stage pN+ at RC			
	OR	95% confidence interval		p value
		lower	upper	
Age at RC (cont.)	0.980	0.973	0.987	<0.001
Clinical tumor stage				
≥cT3 vs. cTa, cTis, cT1	3.367	1.977	5.733	<0.001
cT2 vs. cTa, cTis, cT1	3.476	0.959	12.604	0.058
Presence of hydronephrosis at RC (ref.: absence)	1.844	1.019	3.336	0.043
Tumor stage ≥T3 and/or N+ at CT before RC (ref.: <T3 and N–)	4.378	2.533	7.566	<0.001

tive ability of both nomograms presented by Karakiewicz was not conferrable to patients of the German cohort because the number of locally advanced UCB was underestimated [5]. The authors stated that the development of new models to predict advanced UCB with a higher PA is needed.

We considered additional clinical parameters for the generation of our model: LVI at last TUR-BT before RC, clinical tumor stage according to muscularis propria (≥cT2 vs. cTa, cTis, cT1 without muscularis propria; ≥cT2 vs. cTa, cTis, cT1 with presence of non-tumor-infiltrated muscularis propria), tumor and nodal stage at CT imaging (≥T3 vs. ≤T3 or N+ vs. N–) and the presence of hydronephrosis before RC. The PA was increased by integrating these factors, which are part of routine diagnostic algorithms. It has been shown that the presence of LVI in TUR-BT specimens was significantly associated with pT3/4 and/or pN+ only in univariate analysis ($p = 0.010$). Green et al. [4] demonstrated that the presence of LVI in the TUR-BT specimen is associated with the presence of pN+ stage independently.

Although the presence of LVI in TUR-BT was not an independent predictor in our final model, it may add relevant information for the prediction of advanced tumor stages. Patients with cT2-tumor stage without LVI had a 57.3% probability of pT3/4 and/or pN+ in the final pathological evaluation versus 75.6% in patients with cT2 and detected LVI ($p = 0.027$).

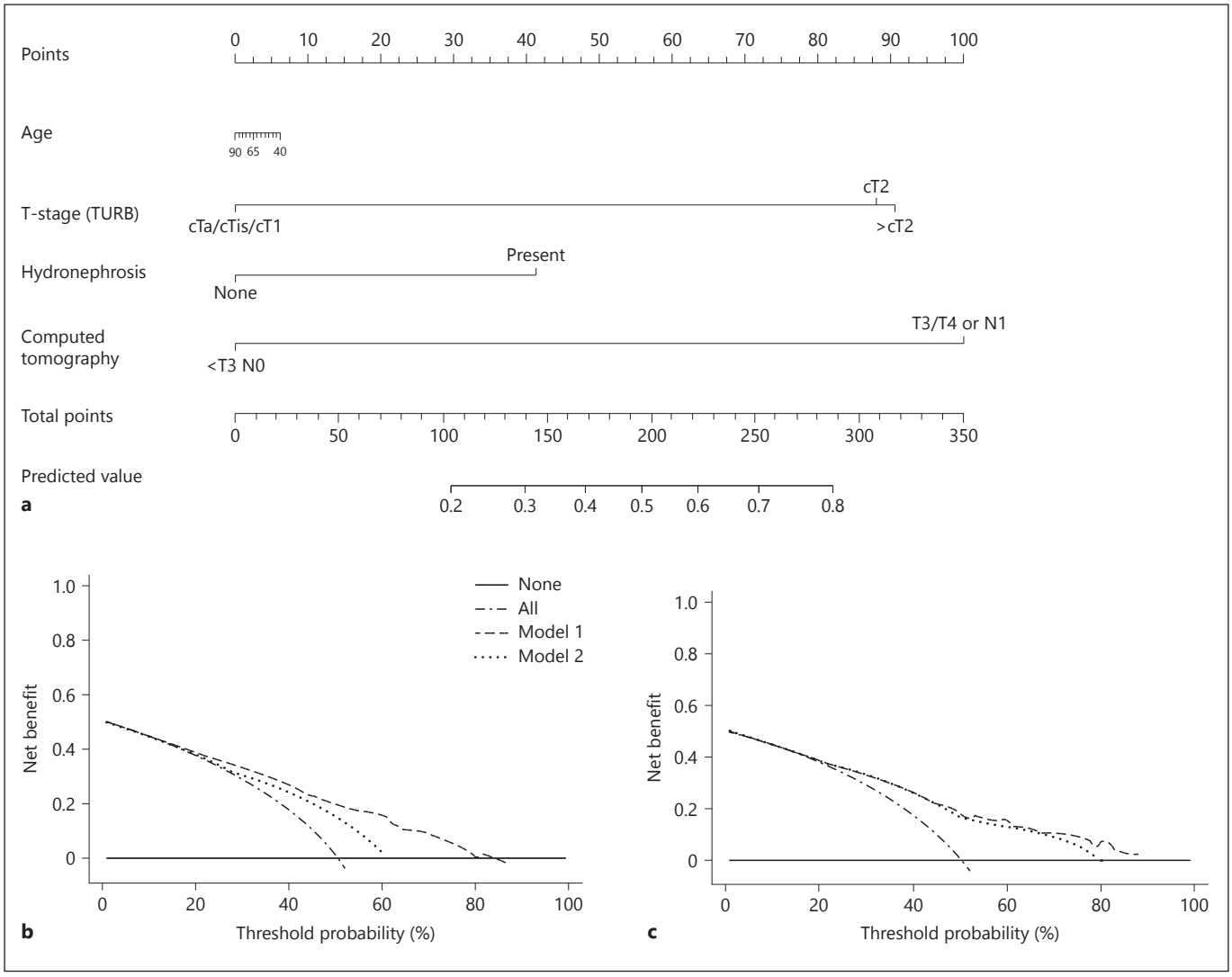

Fig. 1. a Nomogram for the prediction of pT3/4 and/or pN+. To obtain the nomogram-predicted probability of pT3/4 and/or pN+ at RC, locate the patient values on each axis. Draw a vertical line to the 'points'-axis to determine how many points are attributed for each variable value. Add the points of all variables. Locate the sum on the 'total points' line to assess the individual probability of the respective stages at RC. **b** DCA showing the net benefit associated with the use of the models for prediction of pT3/4 and/or pN+ at RC. Model 1 (dashed line) refers to our newly developed nomogram. Model 2 (dotted line) refers to the prediction of pT3/4 and or pN+ according to the variable ≥cT2. **c** DCA showing the net benefit associated with the use of the models for prediction of pT3/4 and/or pN+ at RC. Model 1 (dashed line) refers to our newly developed nomogram. Model 2 (dotted line) refers to the prediction of pT3/4 and or pN+ according to the reduced model (cT-stage of TUR-BT and radiological assessment at CT).

The quality of TUR-BT and related clinical tumor stage plays an important role for the prediction of definite tumor stage. For an improved accuracy of the clinical tumor stage in TUR-BT specimens, we included the presence of a tumor-free muscularis propria in TUR-BT specimens. We discovered that the factor ≥cT2 vs. cTa, cTis, cT1 with the presence of tumor-free muscularis propria was significantly associated with pT3/4 and/or pN+ only in univariate analysis ($p < 0.001$). In our multivariate model, lower patient age was an independent predictor for advanced tumor stage (OR 0.980; $p < 0.001$). This fact is contrary to the results of Karakiewicz et al. [3]. One might conclude that younger patients with MIBC in particular may benefit from an early RC because of their higher probability of having advanced tumor stage.

Considering the important role of modern imaging methods for clinical staging prior to RC, the integration of cT- and cN-stage by preoperative imaging appeared essential when generating our nomogram. In our cohort, an advanced tumor stage on preoperative CT imaging ≥T3 and/or N+ was an independent predictor for tumor stage pT3/4 and/or pN+ (OR 4.378; $p < 0.001$) at RC. Stimson et al. [15] previously described the association of preoperative hydronephrosis with the presence of non-organ-confined UCB with lymph node metastases at the time of RC. In our cohort, the presence of hydronephrosis was identified as an independent predictor for advanced tumor stage pT3/4 and/or pN+ (OR 1.844; $p = 0.043$).

The use of a pre-cystectomy nomogram with a high PA regarding the presence of advanced tumor stages may help the clinician to decide whether or not to apply NAC. NAC may have a beneficial effect by downstaging and reducing the probability of a positive surgical resection margin as well as in an early treatment of potential micrometastases [16, 17]. Grossman et al. [18] demonstrated that patients with locally advanced UCB benefitted from NAC when compared to RC alone in the SWOG S8710 study. Using low risk and high risk features, Culp et al. [19] also identified patients with a poor prognosis who are most likely to benefit from NAC. However, NAC is rarely practiced. Possible reasons for the underutilization of NAC remain still unclear but could be explained by concerns regarding efficacy and potential delay of RC. In a recent study only 12% of the patients with clinical tumor stages pT2-T4aN0M0 received NAC whereas 22% received adjuvant chemotherapy [20]. Similarly, only a small proportion of patients received NAC in the present study: altogether, 7 patients (2.1%) with NAC were included in the study population. A sensitivity analysis of the 330 patients without NAC (data not shown) showed the same results as mentioned above.

This study is limited by the heterogeneous cohort composed by patients treated at different centers in Germany, Austria and Italy with different surgical practices such as extent of lymphadenectomy, histopathological assessment or quality of TUR-BT. Another limitation displays the lack of a standard template of lymph node dissection. However, pelvic lymph node dissection was performed routinely and the extension of the dissection was based on preoperative CT scan and suspicious intraoperative findings. Other important limitations were the lack of a central pathology and radiology review as well as the differences in clinical pathways, postoperative monitoring and follow-up.

Conclusion

We developed a new nomogram for the prediction of locally advanced tumor stage pT3/4 and/or pN+ before RC using established clinicopathological parameters. The high PA and easy application may allow the use of our nomogram in daily clinical practice. An external validation of our model is required.

Acknowledgments

We would like to thank the members of the PROMETRICS 2011 research group for their valuable effort: Christian Gilfrich, Hans-Martin Fritsche, Alexander Buchner, Jörg Ellinger, Isabella Syring, Wolfgang Weidner, Melanie Durschnabel, Günter Janetschek, Christoph Wiesner, Georg Bartsch, Gördük, Murat, Chris Protzel, Rudolf Moritz, Joachim Noldus, Rein-Jüri Palisaar, Vladimir Novotny, Sascha Pahernik, Boris Hadaschik, Roman Mayr, Florian Hartmann, Paul Schramek.

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