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Scoring system development for prediction of extravesical bladder cancer

Razvoj bodovnog sistema u predviđanju ekstravezikalnog karcinoma mokraćne bešike

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Abstract

Background/Aim. Staging of bladder cancer is crucial for optimal management of the disease. However, clinical staging is not perfectly accurate. The aim of this study was to derive a simple scoring system in prediction of pathological advanced muscle-invasive bladder cancer (MIBC). **Methods.** Logistic regression and bootstrap methods were used to create an integer score for estimating the risk in prediction of pathological advanced MIBC using precystectomy clinicopathological data: demographic, initial transurethral resection (TUR) [grade, stage, multiplicity of tumors, lymphovascular invasion (LVI)], hydronephrosis, abdominal and pelvic CT radiography (size of the tumor, tumor base width), and pathological stage after radical cystectomy (RC). Advanced MIBC in surgical specimen was defined as pT3-4 tumor. Receiving operating characteristic (ROC) curve quantified the area under curve (AUC) as predictive accuracy. Clinical usefulness was assessed by using decision curve analysis. **Results.** This single-center retrospective study included 233 adult patients with BC undergoing RC at the Military Medical Academy, Belgrade. Organ confined disease was observed in 101 (43.3%) patients, and 132 (56.7%) had advanced MIBC. In multivariable analysis, 3 risk factors most strongly associated with advanced MIBC: grade of initial TUR [odds ratio (OR) = 4.7], LVI (OR = 2), and hydronephrosis (OR = 3.9). The resultant total possible score ranged from 0 to 15, with the cut-off value of > 8 points, the AUC was 0.795, showing good discriminatory ability. The model showed excellent calibration. Decision curve analysis showed a net benefit across all threshold probabilities and clinical usefulness of the model. **Conclusion.** We developed a unique scoring system which could assist in predicting advanced MIBC in patients before RC. The scoring system showed good performance characteristics and introducing of such a tool into daily clinical decision-making may lead to more appropriate integration of perioperative chemotherapy. Clinical value of this model needs to be further assessed in external validation cohorts.

Key words:
urinary bladder neoplasms; prognosis; factor analysis, statistical; transurethral resection of prostate; neoplasm staging; hydronephrosis.

Apstrakt

Uvod/Cilj. Stadiranje raka mokraćne bešike je od ključne važnosti u optimalnom lečenju bolesti. Kliničko stadiranje, međutim, nije dovoljno pouzdano. Cilj rada bio je da se izvede jednostavan bodovni sistem u predviđanju patološki uznapredovalog, mišićnoinvazivnog raka mokraćne bešike (MIBC). **Metode.** Logistička regresija i samodopunjujuća metoda korišćena je za izradu celobrojnog skora procenjenog rizika predviđanja patološki uznapredovalog MIBC uz pomoć kliničkopatoloških podataka pre učinjene cistektomije: demografskih karakteristika, inicijalne transuretalne resekcije (TUR) tumora mokraćne bešike [gradus, stadijum, brojnost tumora, limfovaskularna invazija (LVI)], prisustva hidronefroze, abdominalne i pelvične kompjuterizovane tomografije (veličina tumora, veličina baze tumora) i patološkog stadiranja nakon učinjene radikalne cistektomije (RC). Uznapredovali MIBC u hirurškom uzorku definisan je nalazom pT3-4 tumora. Prediktivna tačnost je procenjena površinom ispod *receiving operating characteristic* (ROC) krive. Klinička korisnost je procenjena analizom krive odlučivanja. **Rezultati.** Ova jednocentrična retrospektivna studija uključila je 233 odrasla bolesnika sa BC kod kojih je učinjena RC na Vojnomedicinskoj akademiji u Beogradu. Oboljenje ograničeno na organ utvrđeno je kod 101 (43,3%) bolesnika, dok je 132 (56,7%) imalo uznapredovalo oboljenje. U multivarijatnoj analizi tri faktora rizika bila su tesno povezana sa uznapredovalom bolešću: gradus

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inicijalne TUR [(*odds ratio* (OR) = 4,7)], LVI (OR = 2) i hidronefroza (OR = 3,9). Rezultujući ukupan bodovni skor kretao se od 0 do 15 poena sa kritičnom vrednošću iznad 8 poena, a AUC 0.795, ukazujući na dobru diskriminacionu sposobnost. Model je pokazao odličnu kalibraciju. Analiza krive odlučivanja pokazala je neto korist duž svih pragova verovatnoće i kliničku korisnost modela. **Zaključak.** Sastavili smo jedinstven bodovni sistem koji bi mogao pomoći u predviđanju uznapredovalog MIBC kod bolesnika pre učinjene radikalne cistektomije. Bodovni sistem je pokazao dobre performanse. Primena ovakvog sredstva u svakodnevnom kliničkom odlučivanju mogla bi dovesti do adekvatnije integracije preoperativne hemioterapije. Kliničku vrednost ovog modela treba dalje proceniti eksternom validacijom.

Ključne reči:
mokraćna bešika, neoplazme; prognoza; statistička analiza faktora; resekcija prostate, transuretralna; neoplazme, određivanje stadijuma; hidronefroza.

Introduction

Bladder cancer (BC) is the most common urologic cancer in men, the eighth most common malignancy in women and the fifth most common malignancy worldwide. Although new bladder tumors are frequently superficial (60–75%) in nature, many of those (up to 20%) can progress to advanced disease. On the other hand, an essential number of advanced tumors are diagnosed at initial presentation with no prior history of transitional cell carcinoma (TCC).

Staging of BC is crucial for optimal management of the disease. Radical cystectomy (RC) has been established as the primary treatment for localized or regionally advanced invasive bladder tumors, as well as high-risk superficial tumors resistant to intravesical therapy. The oncological outcome after radical surgery highly depends on the extent of the disease: the 5-year survival rate was in the range of 60–81% in pT2 tumor, 17–47% in pT3-4 tumor, and 22–35% in pN+ tumor [1]. A similar situation is found in choosing appropriate cases for extensive pelvic lymph node dissection (PLND). Because of understaging, these patients did not receive neoadjuvant chemotherapy (NACT) that is associated with a potential benefit for this group of patients. Available data shows an absolute survival benefit from NACT of ≈ 5% for patients undergoing RC. However, only a small number of patients with stage III BC actually receive NACT [2]. Furthermore, predicting extravesical disease also aids in patient selection for bladder-preserving approach [1].

Clinical staging based on physical examination, transurethral resection (TUR) pathology and imaging are the most important factors for predicting pathological stage, but unfortunately, predictions are not perfectly accurate. Despite technological improvements, imaging studies are still inaccurate, both in staging of primary tumor as well as in nodal staging [2]. Consequently, clinical prediction has evolved from physician judgment alone to risk group stratification, to prediction models based on multivariate regression or principal component analysis, to nomograms and a decision tree model [1, 3–8].

Several recent studies have demonstrated that multivariate models are more accurate than most informative single predictors such as any TUR staging variable in isolation, clinical staging alone or than techniques of risk group assignment [7]. For better identification of advanced muscle-invasive BC (MIBC), Karakiewicz et al. [4] had developed two nomograms to predict pT3-4 and pN+ disease. Their models, however, failed to retain favorable discrimination ability in a European series [9]. Furthermore, the risk of pT3-4 tumor and lymph node involvement was underestimated in external dataset [9, 10]. At last, pre-surgical models that can accurately predict which patients are likely to have more extensive disease are sparse.

Based on these considerations, the aim of this study was to examine whether a multivariate model expressed in scoring system could generate more accurate stage predictions. To test this, we developed a prognostic model and scoring system to accurately predict advanced pathologic T stage at cystectomy.

Methods

After obtaining institutional review board approval, we retrospectively reviewed medical records of 248 patients who had undergone radical surgery for BC at the Military Medical Academy, Belgrade, Serbia, over the 11-year study period (from January 2002 through December 2012). For each patient, comprehensive clinical and pathologic information was collected as precystectomy assessment. The patients underwent routine cystoscopic and upper tract evaluation, physical examination, TUR of bladder tumor (TURBT), abdominal and pelvic computed tomography (CT) and chest radiography. Evaluation for the presence of hydronephrosis, if any, was performed in all the patients, as previously described [11]. TUR stage was assigned by the operative surgeon according to the 2002 tumor nodes, metastasis (TNM) system. Lymphovascular invasion (LVI) in TURBT or biopsy specimen was defined as the unequivocal presence of tumor cells within the endothelium-lined space, with no underlying muscular walls [12]. The indications for RC were tumor invasion into the *muscularis propria* or prostatic stroma or Ta, T1, or carcinoma *in situ* refractory to TUR with intravesical chemotherapy and/or immunotherapy. No patient received radiotherapy or chemotherapy before RC. The patients with non-urothelial BC, or salvage RC after failed radiotherapy or neoadjuvant chemotherapy, or incomplete data were excluded. No patient had distant metastatic disease at the time of cystectomy. All the patients underwent RC, pelvic lymphadenectomy and urinary diversion [13]. All surgical specimens were processed according to standard pathological procedures and histopathological slides were reviewed by genitourinary pathologists according to the 1973 World Health Organization grading and 2002 American Joint Committee on Cancer TNM staging.

Outcome measures

The presence of advanced MIBC in surgical specimens was the primary interest of statistical analysis. It was defined as pT3-4 tumor with/without lymph node metastases after pathological review.

Predictor variables

The following predictor variables were chosen *a priori* for the defined outcome: demographic data (age, sex), TURBT findings (grade, stage, multiplicity of tumors, LVI), hydronephrosis, abdominal and pelvic CT radiography (tumor size, tumor base width), and pathological stage after RC.

Statistical analyses

Univariate analysis was initially carried out to search for the variables that were statistically significantly associated with potential risk factors for advanced MIBC. Variables that showed statistically significant relationship ($p < 0.05$) were incorporated in the multivariate model. Multiple logistic regression analysis was applied (with Backward–Wald stepwise) to adjust for possible confounders and to identify and quantify the independent extravesical disease predictors. The regression results were expressed in odds ratios (ORs) with 95% confidence interval (CIs). The stability of the model's effect estimates and check for overfitting examined by using the bootstrap method, as previously described [14]. Briefly, we generated 1,000 samples using bootstrapping methods, and then the medians of the resultant beta coefficients for each variable were used for developing an integer based weighted point system for advanced MIBC. The coefficient for each variable was multiplied by 10 and then the result was rounded off to the nearest integer. Each patient-discharge record was assigned the individual scores by summing the individual risk factor points. The best discriminating power was identified by determining the cut-off points for predicting advanced MIBC as the score giving the best Youden index (sensitivity + specificity - 1) for each scoring system. Eventually, the scoring system was applied to test the rule. Prognostic model validation (calibration) was performed by comparing the observed and predicted event rates for groups of patients. Receiver operating characteristic (ROC) curves were used to quantify discrimination, measures that distinguish between patients who experience the event of interest and those who do not [15]. We determined the sensitivity, specificity, overall correctness of prediction, and positive and negative predictive values for scoring systems. Clinical usefulness was assessed by using decision curve analyses [16]. These analyses estimate a ''net benefit'' for prediction models by summing the benefits (true positives) and subtracting the harms (false positives). The latter are weighted by a factor related to the relative harm of a missed advanced MIBC cancer versus an overrated tumor. Assumption is made that identification of advanced MIBC would lead to treatment with NACT. Net benefit is plotted against threshold probabilities compared with "NACT for all" strategy and "NACT for none". The interpretation of a decision curve is that the model with the highest net benefit at a particular threshold probability should be chosen. All analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL) and R-statistics (the R foundation for Statistical Computing, version 2.3.1) and the statistical significance was set at $p < 0.05$.

Results

This retrospective cohort study design examined clinical and pathological descriptive variables of 233 evaluable patients with BC undergoing RC. The mean patient age was 63.8 ± 9.2 years (range 42–86 years). The population comprised 28 (12%) women and, 205 (88%) men. There were 120 (51.5%) patients with primary RC and 113 (48.5%) with secondary RC. Of all the patients, 109 (46.8%) presented with no, 78 (33.5%) unilateral and 46 (19.7%) bilateral obstruction (hydronephrosis). Preoperative size of dominant tumors was median 4.0 cm, interquartile range (IQR) 3.0 cm (range 1–12 cm). In 33 (14.2%) patients there was one, in 37 (15.9%) two, and in 163 (70%) more than two tumors. Tumor base width on CT was median 3.0 cm, IQR 2.0 cm, (range 1–10.0 cm). TUR was performed in 194 (83.3%) patients, median 2 months, IQR 1 month (range 1–12 months) before RC. A total of 197 (84.5%) patients had TUR grade 3 cancers, and 36 (15.5%) TUR grade 2 cancers. At TUR, 12 (5.2%) had Ta or Tis pathologic stage of disease, 46 (19.7%) had T1 stage, and 175 (75.1%) had T2 stage. LVI in TURBT or biopsy specimens was noted in 162 (69.5%) patients.

Pathological staging of the entire cohort was distributed as follows: 1 (0.4%) patient had residual carcinoma *in situ* (CIS), 12 (5.2%) had T1, 88 (37.8%) had T2, 79 (33.9%) had T3, and 53 (22.7%) had T4 disease. Overall, patients were categorized into organ confined (OC) disease (pathological stage < T3: n = 101, 43.3%) versus pathologically advanced MIBC [stage ≥ T3; n =132 (56.7%)].

The clinicopathological characteristics of the patient cohorts (OC or advanced MIBC) are shown in Table 1. Of note, there were no differences in age, gender, primary or secondary RC, number of tumors between those OC *versus* those who were not.

In univariate analysis, 6 risk factors displayed a significant correlation with advanced MIBC (Table 2). During multivariate analysis that included these 6 parameters as covariates, three sustained their prognostic significance (Table 2). The analysis demonstrated the initial tumor grade, LVI and hydronephrosis had strong prognostic value of advanced MIBC. All variables maintained significance in the bootstrap model; thus, the model was considered to be reliable and not over-fit. The Hosmer and Lemeshow goodness of fit test statistic was $p = 0.285$, thereby demonstrating good fit. The Brier score for a model was 0.1762. The Nagelkerke's R^2 value which indicates the percentage of variation of the outcome explained by the predictors in the model was 0.3767. A coefficient of reliability (Cronbach's alpha) was 0.6619 that was considered acceptable.

Next, a total score was calculated by summing the points from each variable for each patient. The resultant total

Table 1

Baseline patients (n = 233) clinicopathological characteristics in organ confined and muscle-invasive bladder cancer (MIBC)

Characteristics	Organ confined disease	Advanced MIBC	*p*
Age (years), $\bar{x} \pm SD$	63 ± 9.4	64.4 ± 8.9	0.262
Gender: female/male, n (%)	15/86 (14.9)	13/119 (9.8)	0.310
Primary/secondary, n (%)	51/50 (50.5)	62/70 (47)	0.600
Size of tumors (median), cm	3.3	5.2	0.000*
Number of tumors: 1/ 2/ ≥ 3, n (%)	11/18/72 (10.9/17.8/71.3)	22/19/91 (16.7/14.4/68.9)	0.403
Initial tumor grade: 2 or 3, n (%)	30/71 (29.7)	6/126 (4.5)	0.000*
Initial tumor stage: Ta/T1/T2, n (%)	6/30/65 (5.9/29.7/64.4)	6/16/110 (4.5/12.1/83.3)	0.030*
Lymphovascular invasion no/yes, n (%)	47/54 (46.5)	24/108 (18.2)	0.000*
Hydronephrosis: no/unilateral/bilateral, n (%)	70/30/1 (69.3/29.7/1)	39/48/45 (29.5/36.4/34.1)	0.000*
Base width on CT (cm)	2; 2.75	3; 2	0.000*

*** Statistically significant difference ($p < 0.05$); CT – computed tomography.**

Table 2

Analysis of possible and independent predictors for advanced muscle-invasive bladder cancer (MIBC) and point values

Risk factors	Univariate analysis		Multivariate analysis		Bootstrap		Point value
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	B	B	
Size of tumors	1.361 (1.181–1.650)	0.000					
Initial tumor grade	8.872 (3.523–22.339)	0.000	4.697 (1.74–12.682)	0.002	1.547	0.099	2
Initial tumor stage	1.932 (1.194–3.126)	0.007					
Lymphovascular invasion	3.917 (2.170–7.068)	0.000	2.026 (1.026–4.004)	0.042	0.706	0.154	3
Hydronephrosis	4.593 (2.908–7.253)	0.000	3.867 (2.284–6.274)	0.000	1.353	0.254	5
Base width on CT	1.510 (1.260–1.809)	0.000					

CT – computed tomography; OR – odds ratio; CI – confidence interval

possible score ranged from 0 to 15, with a cut-off value of > 8 points. The areas under the ROC curve for the model was 0.818, (95% CI 0.764–0.871), showing the model to have good discriminatory ability. In internal validation, after adjusting for overfitting the scoring system achieved a bootstrap-corrected area under curve (AUC) of 0.795 (95% CI 0.739–0.851) (Figure 1), and the discrimination ability was only slightly decreased (0.023), indicating a successfully built robust model. The sensitivity was 68.9% (95% CI 60–76.7%), the specificity was 72.3% (95% CI 62.5–80.7%), the positive predictive value was 76.5%, whereas the negative predictive value was 64%. In other words, a score of less than or equal to 8 correctly identified OC disease in 73 of 101 patients (72.3%), whereas a score of more than 8 correctly identified advanced MIBC in 91 of 132 patients (68.9%). Graphical assessments of score calibration are presented in Figure 2. The scoring system was well calibrated ($R^2 = 0.825$).

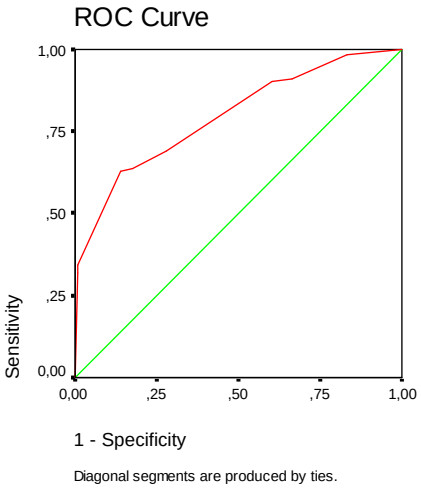

Fig. 1 – Receiver operating characteristic (ROC) curve analysis scoring system for predicted advanced muscle-invasive bladder cancer.

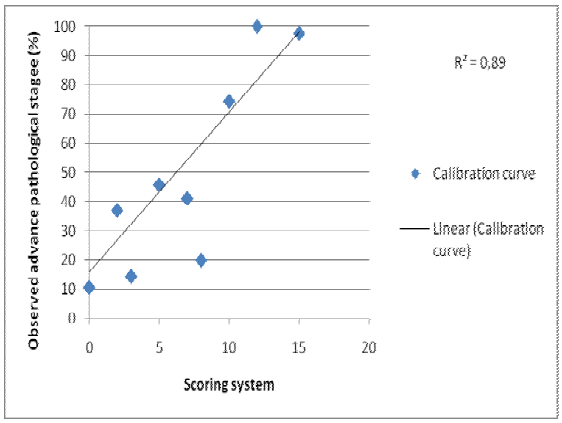

Fig. 2 – Observed *versus* predicted advanced muscle-invasive bladder cancer by score.

In the decision curve analysis (Figure 3), the model predicting advanced MIBC provided a net benefit throughout the entire range of threshold probabilities as compared with the strategy of treating all patients with NACT, or alternatively, treating no one. The graph shows that the final model leads to the highest net benefit (dotted black line) compared to the models including only tumor grade (dotted red line) or only LVI (dotted green line).

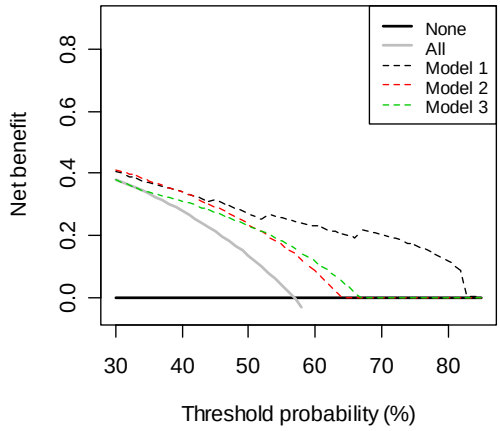

Fig. 3 – Decision curve analysis of the effect of prediction models on detection of advanced muscle-invasive bladder cancer (MIBC). Net benefit is plotted against various threshold probabilities. The model 1 is the final model including initial tumor grade, lymphovascular invasion and hydronephrosis (dotted black line). The model 2 is a model including only tumor grade (dotted red line). The model 3 is a model including only lymphovascular invasion (dotted green line).

Discussion

The most significant prognostic factor in patients undergoing RC for MIBC is the pathologic stage. It has been reported that the rate of clinical understaging is as high as 50% [7, 10]. Consequently, the need to improve pathological stage prediction is of great importance.

In the present study, exceptional approach was used to applying a scoring system, a mathematic tool, without the need for statistical software for interpretation/prediction to achieve an improvement in pathologic stage prediction before RC in the individual patient. By combining known clinicopathological prognostic factors, our model was able to achieve an accuracy of 79.5%. Various measures of model fit (discrimination, calibration) showed a good predictive ability and clinical usefulness in the internal validation.

To date, several clinicopathological factors have been reportedly associated with post-surgical pathological stage and were included in the existing models such as TUR parameters of stage and grade [1–4, 7, 8], LVI [1–3, 6], hydronephrosis [3, 6–8], age [4, 6, 8], female gender [2, 4], CIS [4], histological variants [2], tumor size [7], tumor growth pattern [8], multiplicity of tumors [6, 8], palpable mass [6], number of intravesical treatments [6], NACT [4], primary versus secondary RC [17], oncofetal markers [7]. We found that LVI at TURBT to be strongly associated with advanced MIBC, that in accordance with previous studies, that have determined LVI to be a strong independent predictor of upstaging, poor clinical outcome [18], nodal invasion and survival in patients undergoing RC [19]. Although LVI was less commonly found in TUR samples than in RC specimens, the pathological feature is strongly suggestive of advanced MIBC [20] and pathologists should be encouraged to report LVI in TURBT pathological reports as it has a direct impact on patients staging and prognosis.

Similar to report by Karakiewicz et al. [4], variables of TUR parameters (stage and grade) have reached statistical significance in univariate or multivariate analysis in our model. However, Shariat et al. [21] reported only 35.7% agreement between TUR stage and surgical stage in patients with BC. They reported pathological upstaging in 42% and pathological downstaging in 22% of their patients. It is known that different quality of TUR reportedly leads to variation in clinical staging from 5% to 70% and may adversely affect the adequacy of biopsy specimens and the reproducibility of the current staging models [6]. In addition, different interpretations of histological findings on TUR specimens among pathologists may have an impact on the accuracy of TUR-related variables. Moreover, in this study initial TURBC was not performed in all of our patients and the above noted may explain why this variable did not demonstrate an independent effect in our study. There is a strong correlation between tumor grade and stage, and most poorly differentiated tumors being muscle and deeply invasive at pathological stage. These tumors have not only a risk of invasion, but also a significant risk of recurrence, progression and cancer-specific mortality rates both noninvasive and invasive BC [22]. It is not surprising that the histologic grades of urothelial carcinoma of the bladder in our model are a crucial prognosticator, and have the independent prognostic significance in prediction of advanced MIBC.

Karakiewicz et al. [4] included TUR parameters of stage and grade, the presence of carcinoma *in situ*, patient age and sex, and treatment with neoadjuvant chemotherapy to predict both a pathologic stage of T3 and lymph node-positive disease in 726 cystectomy patients. Their model indicated the accuracy of 76% for patients with advanced T-classification. However, a recent validation study in European patients, demonstrated a notable decrease in model performance: the AUC was 67.5% for pT3-4 disease and 54.5% for pN+ disease [9]. Therefore, our model included additional clinical parameters known to predict pathologic outcome such as hydronephrosis. These findings support those of previous investigators such as Stimson et al. [23], who reported that preoperative hydronephrosis was independently associated with extravesical and node-positive disease at the time of cystectomy. Similar to another report [8], hydronephrosis was the first-tier discriminator in predicting extravesical disease. We found that abnormal imaging was a strong independent predictor and control for other predictors, those patients with hydronephrosis had nearly fourfold increases in the risk of advanced MIBC. The independent prognostic value of hydronephrosis was further confirmed in another series of cT2 disease as predictor of extravesical disease [24]. Incorporating

these factors in our scoring system resulted in the AUC of 0.79, which is statistically better than a model including only variables proposed by Karakiewicz et al. [4] and similar to other reports (0.79–0.85) [1, 3, 6, 7].

In most previous studies on pathologic stage prediction only patients with clinically OC MIBC [1, 3, 6–8] were analyzed, but they were only a subpopulation of patients with BC invading bladder muscles and candidate for RC. However, in our study a broader population was incorporated, and subsequently included patients diagnosed as having clinical T3 and T4 disease considering that clinical prediction is of limited accuracy, and that RC is standard treatment for T3, but also in some T4 disease [25]. Our results are in agreement with recently reported findings [17] that patients who undergo secondary RC (for recurrent/progressive disease after initial bladder sparing modalities) have more favorable pathology at the time of cystectomy and are understaged to a lesser degree than patients who receive a primary RC.

This study has several limitations worth noting. First, the enrolled patients were retrospectively collected in a single tertiary center with a relatively small patient cohort who may influence the results by the selection bias. Second, we examined extravesical disease extension which is a useful intermediate endpoint. However, more clinically significant endpoints are predicting disease outcome or response to therapy and it will be the focus of future studies. Additionally, the study did not include other possible risk factors for advanced disease, such as biomarkers, [7] bimanual palpations [26]. These data were not available in our cohort. In BC, although not yet part of routine clinical assessment, multiple biomarkers have been identified, including urine, immunohistochemical, and abnormal levels of serum oncofetal markers before cystectomy, that in combination with other known clinical prognostic factors could achieve enhanced preoperative prediction of pathologic staging (reported 85% accuracy in predicting extravesical BC) and were associated with adverse pathologic outcome, poor outcome and reduced survival [7]. On the other hand, lack of sufficient data on bimanual palpation could indicate that most current urologists are relying more and more on these pelvic imaging techniques during the clinical staging process and in accordance with the observed decrease in the number of bimanual palpation performed in the last decades. Furthermore, bimanual palpation is a subjective measure, and depends on both the experience of the surgeon and the physical constitution of the patient [26]. Our models are not applicable to patients who were pretreated with radiotherapy or to those harboring pathologies other than transitional cell carcinoma. In addition, we used a bootstrap method internal validation and did not use an external cohort to validate our scoring system. Nevertheless, the prediction model represents another step toward accurately estimating individualized risk of advanced MIBC in a patient population lacking optimal staging procedures.

Conclusion

Using a panel of clinicopathological features obtained before radical surgery, we developed a unique scoring system, simple user-friendly, to assist in predicting advanced muscle-invasive bladder cancer in patients before radical cystectomy. The newly devised formula has the accuracy of 79.5% and has been internally validated. Adoption of such a tool into daily clinical decision-making may lead to more appropriate integration of perioperative chemotherapy, thereby potentially improving survival in patients with bladder cancer. Further external validation in a large cohort is necessary. The clinical value of this model needs to be further assessed in external multi-institutional validation cohorts.

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